MEDICAL REVIEW OF SPONSOR'S COMPLETE RESPONSE TO CR LETTER – Final Review

STN 125287/0/25

PRODUCT: C1-ESTERASE INHIBITOR (HUMAN), BERINERT P

DATE RECEIVED BY FDA: 10 April 2009, amended several times

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Short Glossary

Study Rescue Medication: Blinded Berinert C1-Esterase Inhibitor or Placebo given as rescue medication (permitted at subject/investigator discretion after 4 hours from Time of start of blinded randomized study medication (ToS)

Any Rescue Medication: Includes study rescue medication as well as analgesics or anti-emetics and medications "non-permitted," according to the protocol

"Non-permitted" = forbidden medications: Open label C1 Esterase Inhibitor, fresh frozen plasma (or PPC), medications targeting any of the mechanisms of action of C1-Esterase **inhibitor; or** Androgens, Tranexamic Acid and Aminocaproic Acid (the last 3 only if their dose changed during the time period of interest in the trial).

ToS: Time of start of blinded randomized study medication

ToSRel: Time of start of relief of symptoms

TtRel: Time between ToS and start of relief of symptoms

ToRes: Time of complete resolution of symptom**s**

TtRel+ = TtRelP: Time between ToS and time of start of relief of symptoms without use of rescue medication; 24 hours as a poor failure outcome for subjects who receive "any rescue medication." The primary endpoint of the pivotal randomized, DB, PC trial is based on TtRel+ (TtRelP).

EXECUTIVE SUMMARY

In this complete response to FDA's complete review letter, the sponsor has submitted revised datasets for their pivotal double-blind, placebo-controlled dose-ranging study, as well as many

supporting source documents relating to prohibited medications, analgesics, and anti-emetics whose use tends to confound the interpretation of efficacy of the test product. The protocol and SAPs contained algorithms for imputing poor/failure values of 24 hours for the primary endpoint, "time to start of relief of HAE symptoms (TosRel)," for when any of these potentially confounding medications were taken prior to TosRel. When imputation based on concomitant medication use was taken into account, ToSRel is designated ToSRelP (or TosRel+), which forms the basis of the Kaplan-Meier curves of the primary endpoint in the package insert.

Revisions to the databases submitted in amendments 25 and beyond were largely related to FDA-requested sponsor review of hospital source records for concomitant medications that may potentially confound the efficacy evaluation. The sponsor has submitted new analyses of the primary endpoint of the pivotal trial using the new datasets. These include both the analysis method (designed by the sponsor as "original analysis") described in SAP version 2.0, which the sponsor confirms was never submitted to the IND or otherwise shared with FDA prior to implantation, as well as what the sponsor terms the FDA-requested "robustness analysis." The latter is regarded as the key primary analysis by the FDA because it more closely follows the protocol.

This SAP version 2.0 was dated 1 week prior to unblinding of the study. The FDA-requested robustness analysis imputes a 24 hour "poor/failure" value for subjects who received non-narcotic as well as narcotic analgesics or anti-emetics between 5 hours prior to ToS and ToSRel, which is in keeping with the spirit of the protocol, as well as for subjects who received any medications "non-permitted" by the protocol within the same FDA-defined time window of interest.

The sponsor's analyses based on the revised datasets continue to support the efficacy of the product. The CBER Biostatistical team has obtained p values smaller than that obtained by the sponsor using a FDA-edited database. FDA edits to ToSRelP values were made on the basis of a blinded review by this reviewer of sponsor-submited source documents pertaining to use of forbidden medications, and discouraged analgesics and anti-emetics whose use factors into the primary analysis according (collectively) to the protocol and SAPs.

During the 2nd review cycle, FDA re-requested the sponsor submit a single dataset with all needed fields for the analysis and more detailed analysis instructions in a stand-alone document to facilitate this process. The sponsor responded to this late in the 2nd review cycle. FDA review of source document concomitant medication record copies included in amendment 25 and comparison of these to Listing Q5B3b and relevant datasets contained in amendment 25 revealed a large number of missing source documents. At FDA request, the sponsor submitted additional source documents on 31 Aug 2009 and still more subsequently. FDA discovered in reviewing the source documents that very few subjects were treated with study test product in the hospital but rather were mostly treated in clinics. This evidently impacted negatively the quality of the medication source documents, as very few source documents have been submitted that unambiguously establish whether concomitant medications whose classes and actions were identified in the protocol as potentially confounding the evaluation of efficacy of the test product were administered during the time period from 5 hours prior to when randomized masked study test medication was given (ToS) and self-reported start of relief of HAE attack symptoms

(ToSRel). An assessment of whether potentially confounding concomitant medications were taken during this time period was needed in order to conduct the primary analysis.

This reviewer has performed a masked review of the submitted source documents and has provided the CBER biostatistician with a -b(4)--- data file titled "Berinert-Imputation-Concom-Meds-X-Rescue" containing fields which indicate whether imputation of a "poor/failure" value of 24 hours should be performed for the primary efficacy analysis of the pivotal trial (in keeping with the pivotal trial protocol and the intent of the sponsor's initial Statistical Analysis Plan). **For the key FDA analysis of the pivotal study's primary endpoint, the CBER biostatistician obtained a p value of 0.0016.** This was actually smaller than the sponsor's p value of 0.014 for the "FDA Robustness analysis," which we consider to be the key sponsor analysis of the primary endpoint. Differences in sponsor and FDA p values are at least in part attributable to the sponsor imputing a poor/failure value of 24 hours due to use of "discouraged" medications, where there were statements in the provided source documents indicating that such medications were not, or were probably not taken between 5 hours prior to randomized study drug was administered and time to initial relief of symptoms. When using the sponsor's unedited datasets, the FDA biostatistician was able to reproduce the sponsor's 1-sided p value for the primary analysis of 0.014 (The sponsor refers to this as the FDA robustness analysis, because it imputes a poor/failure value of 24 hours if subjects took either narcotic or non-narcotic analgesics between -5 hours and ToSRel). The sponsor also redid its "original" primary endpoint analysis based on the revised database, not imputing 24 hours for subjects only on the basis of having taken non-narcotic analgesics during this time period of interest.

In cases where the source documents bear a statement apparently written contemporaneously with the dates of the trial indicating that no medications were taken by the subject during the period 5 hours prior to ToS, a 24 hour value for the primary endpoint has not been imputed in the FDA analyses, provided no record was submitted indicating that "non-permitted" medication or narcotic or non-narcotic analgesics or medicines with anti-emetic properties were taken in the clinic or hospital prior to ToS.

If the source documents leave doubt as to whether one or more "non-permitted" medications or narcotics or non-narcotic analgesics or medicines with anti-emetic properties started prior to the trial and marked as "Ongoing" on the CRFs and source documents (SDs) may have been taken between – 5 hours and ToS, the FDA statistician has performed 2 additional robustness analyses of the primary endpoint, which gave values of 0.0004 and 0.0053.

In many cases, doubt as to whether such potentially confounding medication(s) may have been taken during this time period of interest exists because it is not clear that the study site personnel necessarily were cognizant of the large number of potentially-confounding medications on the sponsor's list of such medications contained in SAP version 2.0. This list of potentially confounding medications was never incorporated into the protocol, for example as an appendix, or added to the CRF, as promised in the protocol. Rather, a preliminary list (not the final list) of such medications was provided to investigators while the trial was ongoing. However, the BiMo inspection reports did not comment on observing this list at any of the inspected study sites. That is why FDA performed 2 robustness analyses to account for different interpretations of source documents concerning whether "any rescue medication" was taken during the period of interest,

prior to ToSRel. It is highly plausible, for example, that study site personnel completing concomitant medication records may not have regarded antihistamines as having anti-emetic properties (the sponsor considers they have such properties) and the study sites may not have considered that non-narcotic analgesics were considered "non-permitted" medications, given that exclusion criterion 15 of the protocol required that narcotic analgesics and anti-emetics not be taken from the onset of the attack. The protocol's primary analysis, however, did not distinguish between narcotic and non-narcotic analgesics when imputing a "poor/failure" value of 24 hours for the primary endpoint if such medications were taken prior to TtRel (time to initial relief of symptoms). As it turned out, in the key FDA analysis of the primary endpoint, there were only 2 subjects for whom a poor/failure value of TtRelP was imputed solely because it appeared that the subject had taken or may have taken a non-narcotic analgesic between -5 hours and time of randomized study medication administration.

In addition to a 1-sided p value < 0.0249 for the primary endpoint, the protocol required that, for the study to be considered successful, at least one of two secondary endpoints (either the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with Berinert compared to baseline, or the number of vomiting episodes within 4 hours after start of study treatment) demonstrate a trend in favor of the high dose Berinert group over placebo, with a one-sided p value of < 0.1.

The FDA statistician points out in her review that the protocol's original interim analysis plan was not followed, in that the sponsor did not revise the sample size of the study upward from 25 subjects per arm to 100 subjects per arm, but rather stopped enrollment after ~ 43 subjects were enrolled into each of the high dose and placebo arms. This reviewer regards the fact that the study achieved a high degree of statistically significant difference between high dose and placebo groups (the primary analysis) for the primary endpoint despite a final sample size less than half that recommended on the basis of the first interim analysis, actually provides reasonable confidence that the product is effective.

FDA concurred with the DSMB's recommendation to stop enrollment in the low dose arm after the interim analysis during the IND phase, but because of a lag in IRB approvals of the amendment ending enrollment in the low dose arm, nearly as many low dose subjects were enrolled as high dose subjects. Thus, the sponsor's finding that the study failed to find a statistically significant difference in the primary endpoint between low dose (10 Unit/kg) and placebo groups, is of particular interest, especially because 10 U/kg has been the standard dose of the product used in Europe. The pivotal study did not support the efficacy of the 10 U/kg dose studied in the low dose group of the pivotal trial. This points out the utility of dose ranging studies, even with products that may have had a considerable period of foreign marketing experience.

Based on the information provided in amendment 25 and beyond during this 2nd review cycle, the safety profile of the product continues to appear acceptable. Because, as noted in the original review cycle medical review memo, (a) the product has been associated with a small number of viral seroconversions for which the causal link to product use was inclusive, (b) there is a substantial incidence of treatment-emergent anti-C1-Esterase Inhibitor antibody detection (thus far non-neutralizing), and (c) thrombolic events, including fatal events, related to the product were observed at doses higher than recommended for HAE attacks in a pediatric trial of patients on

cardiopulmonary bypass, FDA requested and the sponsor agreed to a PMC to establish a registry which will capture ADRs among all subjects treated with Berinert for any indication, including seroconversions, hypersensitivity reactions, and thromboembolic events.

RECOMMENDATION:

This Berinert original BLA, as amended, may be licensed from the medical perspective.

CBER's CR Letter Clinical Items followed by Sponsor's Responses (in italics) and Reviewer Comments (in bold)

5. Based on the information provided to date in your original BLA and amendments, we have been unable to validate that your primary endpoint analyses have been conducted according to the protocol and/or statistical analysis plan. For example:

    - The protocol indicates that subjects who received analgesics or anti-emetics prior to reporting their time to start of relief of symptoms were to have a "poor/failure" value of 24 hours imputed for the primary endpoint variable. We note that for variables "CMSTDI" (Start Date of Medication -b(4)- date), "CMSTTI" (Start Time [of concomitant medication]), and "TOANALG" ("Date/Time of first analgesic after start of first administration in the respective time window" and "time of start of analgesics/anti-emetics/C1 INH/FFP") in the ADCM concomitant medications database, there are large numbers of concomitant medications with analgesic or anti-emetic pharmacologic properties for which the values of one or all these key variables are missing.

Sponsor's Response

CSLB Response 5A:

Introduction – Study Conduct and Analysis According to Protocol

When conducting the primary endpoint analyses of the study, CSLB strictly adhered to the study protocol and the Statistical Analysis Plan (SAP) that was prepared and signed off well prior to initiating any data analyses, as detailed in the following subsections:

CSLB's Interpretation/Understanding of the Term "Pain Medication"

Please refer to the Cover Letter (in CDROM subfolder 1_Cover Letter + Attachments A, B, C) that contains CSLB's and outside consultants' positions concerning the use of non-narcotic pain medications for the treatment of acute HAE attacks.

Because non-narcotic pain medications are regarded as ineffective for the treatment of acute HAE attacks, CSLB restricted the term "pain medication" to denote narcotic pain medications in the study protocol and the SAP.

To verify and track the use of prohibited medication, a prohibited medication list was prepared and updated with the new medications that were administered in the course of study conduct. This

list consequently only contained narcotic pain medications. The same list was included in the SAPs for the interim and final analyses (see CDROM subfolder Attachment 8 for SAPs) to perform the imputation of a poor/failure outcome of 24 hours if any of the specified prohibited medications was given in the critical time window for efficacy assessment. The prohibited medication list in Appendix IVa of the SAP for the final analysis, Version 2.0 dated 26 October 2007, was the basis for the original analyses of the primary endpoint.
Therefore, the use of non-narcotic pain medication administration was not defined as an exclusion criterion and not taken into account for the primary endpoint analyses, unlike the use of prohibited narcotic pain medications that resulted in the imputation of a poor/failure outcome.

In order to clarify the reasons for the missing values pointed out in *CBER Comment 5A*, the variables in the concomitant medications dataset ADCM (original database of safety follow-up; location: CDROM subfolder *3_Datasets and Programs\3.2_Original database safety follow-up;* additionally located in CDROM subfolder *Attachment 5A*) are explained below:

(1) Data recorded by the investigator on the case report form (CRF):
For each concomitant medication, the investigator was to document the following items on the "Prior/concomitant medication" CRF with respect to timing of administration:

- "Check if drug started prior to study" (variable ZPRIOR);
- Start date (variable CMSTDTF) and start time (variable CMSTTMF);
- "Check if ongoing" (variable CMONGO);
- End date (variable CMENDTF).

(2) Investigator comments:
The concomitant medications dataset ADCM also includes the investigator comments (variable INVCMT) confirming that prohibited concomitant medications (i.e., according to Appendix IVa of final SAP, Version 2.0) documented as "prior" and "ongoing" on the Prior/concomitant medication CRF were not administered in the queried, critical time period. This means that the variable INVCMT only contains a value if the investigator confirmed (in response to a query) that the prohibited concomitant medication was <u>not</u> administered during the queried, critical time period. For details on CSLB's queries sent to investigators and the investigators' responses, please refer to CSLB Response 5B1+5B2.

(c) The variable TOANALG in dataset ADCM represents the start date (HELPS) and time (HELPTI) of administration of prohibited medications and was only derived under the following conditions:

- *For analgesics, anti-emetics, open-label C1-INH or fresh frozen plasma (FFP), as listed in Appendix IVa of the SAP for the final analysis, Version 2.0 (located in CDROM subfolder Attachment 8);*
- *If the aforementioned prohibited medications were administered between start of study medication (ToS) and 24 hours thereafter.*

As a consequence, TOANALG is missing in all other cases. In particular, TOANALG was not derived:

- *For non-narcotic pain medications (such as aspirin, etc) that were not part of the prohibited medication list in SAP, Version 2.0, Appendix IVa. Please refer to the Cover Letter (located in CDROM subfolder 1_Cover Letter + Attachments A, B, C) that provides CSLB's and outside consultants' positions concerning the ineffectiveness of non-narcotic analgesics in the treatment of acute HAE attacks.*
- *For medications given only prior to start of study medication, i.e., with an end date (HELPE) prior to start of study medication.*
- *If the investigator comment (variable INVCMT) confirmed that the prohibited medication in question was not used between start of study medication and start of symptom relief.*

In the datasets other than ADCM that use TOANALG on a subject level, the earliest TOANALG (i.e., minimum TOANALG) was taken into account for this subject for calculation of the primary endpoint, time to start of symptom relief (TtRel+). See the Reviewer Guide to the Database for the two different definitions of TtRel+ used in the original analysis and the additional robustness analysis conducted to address *CBER Comment 5C* (location: CDROM subfolder *3_Datasets and Programs\3.1_Reviewer Guide to Database*).

(4) Impact of prohibited concomitant medications on the primary endpoint TtRel+:
One of the pre-specified reasons to set the primary endpoint TtRel+ to a poor/failure outcome of 24 hours was the administration of narcotic analgesics, anti-emetics, open-label C1-INH or FFP between ToS and ToSRel. If TOANALG contains a value (based on the criteria described in point 3c) on the previous page) and if TOANALG occurred before ToSRel, then TtRel+ was set to a poor/failure outcome of 24 hours.

Of note, the variable TOANALG does not reflect any of the other reasons for setting TtRel+ to a poor/failure outcome (i.e., administration of rescue study medication or missing ToSRel value).

Reviewer Comment

As documented in the sponsor's response to CR item 8, the sponsor never submitted version 2.0 of the SAP, i.e., the version the sponsor used in their original BLA submission analyses, to the IND. Because the sponsor did not document at the time the SAP version 2.0 was written the reasons certain forbidden medications and pain reliever medications were to result in imputation of a "poor/failure" 24 hour value for the primary endpoint variable, time to initial relief of symptoms (TTRELP), I do not consider primary endpoint analyses following SAP version 2.0 to be valid. The FDA review will focus on the re-analysis of the primary endpoint requested in the CR letter, which imputes a (> 4 hour or) 24 hour value for the primary endpoint for subjects who were documented to have taken "any rescue medication," meaning any of the "forbidden" medications listed in the protocol, or any (narcotic or non-narcotic) analgesic or anti-emetic any time in the time window from 5 hours prior to the start of study test medication to time to initial relief of symptoms. (Androgens, tranexamic acid, and amino caproic acid use during this time frame would only

result in a 24 hour imputation for the primary endpoint if the dose had increased). The sponsor calls this analysis the "robustness" analysis and has created various robustness analysis datasets for this analysis.

The 3 consultants' letters indicate the authors are unaware of any published information that bear on whether non-narcotic analgesics, including ASA, NSAIDs, and acetaminophen, may affect the intensity of any abdominal HAE symptoms. The physician consultants' letters do not address the question, raised by FDA in the CR letter, as to whether any facial HAE attack symptoms, such as facial tightness, might be affected by non-narcotic analgesics. The head of the HAE patient organization states in his letter he is unaware of any HAE patient who has ever discussed with his/her physician whether non-narcotic analgesics may affect the intensity of HAE symptoms. Note that whether non-narcotic analgesics are capable of causing complete relief from HAE attack symptoms is not at issue. Rather, because the primary endpoint relates to initial (i.e., partial) relief of symptoms, what is at issue is whether non-narcotic may moderate the intensity of any type of abdominal or facial HAE attack symptom, even to a mild, but perceptible degree. In the absence of controlled clinical data to resolve this question, the FDA analysis of the primary endpoint will emphasize imputation of a "poor/failure" value of > 4 hours or 24 hours for subjects who were documented to have taken any narcotic or non-narcotic pain reliever, anti-emetic, or forbidden medication ("any rescue medication") in the pertinent time window. FDA and the sponsor also gave consideration to showing the result of an analysis that excludes non-narcotic analgesics from such "poor/failure" imputations, as a robustness analysis (which I shall call the R2 analysis), however the results of this analysis turned out to be similar to that of the "robustness" analysis, because only 2 subjects in the FDA key primary endpoint analysis were imputed a 24 hour value solely because of use of non-narcotic analgesics.

The sponsor's statement, "Because non-narcotic pain medications are regarded as ineffective for the treatment of acute HAE attacks, CSLB restricted the term "pain medication" to denote *narcotic* pain medications in the study protocol…" is inaccurate:

The protocol stated on p 21 under the heading "<u>Pain medication and anti-emetics</u>"

"Due to potential interference with assessment of the primary efficacy variable, the use of pain medication (*meaning narcotic pain medication*) and anti-emetics is strongly discouraged during the acute phase of treatment. If possible, these medications should not be used until at least four hours after start of study medication administration.

Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received these types of medications listed in the CRF."

On p 35 of the protocol under section 7.3.1 (Analysis of efficacy – Primary efficacy criterion) it states that "Then the primary efficacy variable is defined as:

(i) TtRel+ = 24 hours (poor/failure outcome), if

- **the subject has received rescue study medication before ToSRel was reached**
- **the subject has received analgesics/anti-emetics before ToSRel was reached,**

-ToSRel – ToS > 24 hours,
Or ToSRel cannot be determined because of missing values

(ii) ToSRel – ToS, otherwise

[where ToS = Time of start of study treatment and
ToSRel – time of start of relief of symptoms]

It is correct that use of narcotic analgesics, rather than all analgesics, taken between start of attack and administration of study treatment, was a protocol exclusion criterion. However, the definition of the primary endpoint used the terms analgesics and pain medication without restricting these to narcotic analgesics. While the sponsor asserts they meant narcotic analgesics, the sponsor has not offered any convincing evidence to know that was the case at the time the protocol was written.

The sponsor's use of the derived variable, TOANALG in the original BLA submission and in the re-analysis submitted in response to the CR letter using the original analysis method is judged to not be sufficiently conservative because

(1) it does not use the complete list of forbidden medications listed in the protocol (use of epsilon amino caproic acid, tranexamic acid, and products (other than FFP and C1-INH) which share a mechanism of action with C1-Esterase Inhibitor,

(2) it does not take into account non-narcotic analgesics, and

(3) it records a 24 hour value only if narcotic analgesics, anti-emetics, open-label C1-INH or FFP were between ToS and ToSRel. If "any rescue medication" were taken shortly before ToS they could confound interpretation of the study endpoints. For this reason, FDA established in the CR letter a relevant timeframe for the re-analysis of the primary endpoint of "any rescue medication" being taken anytime from 5 hours prior to ToS to ToSRel (for the primary endpoint) or from 5 hours prior to ToS to time to complete relief of symptoms for the latter study variable. Note that the protocol demanded that narcotic analgesics and anti-emetics not be taken between start of attack and 4 hours after ToS. In a large number of cases, start of attack was > 5 hours prior to ToS.

- We understand from our telephone conversation held on November 12, 2008 with representatives of your firm and --b(4)-----, your Contract Research Organization which performed statistical analyses for this BLA, that some investigators had indicated on the original CRFs (Case Report Forms) for a number of anti-emetics, analgesics, and/or medications "Non-permitted" by the protocol until after complete

resolution of the HAE attack, for several subjects, these medications were being taken at screening and were marked as "continuing" to be administered. You indicated during the teleconference that, in these instances, you sent the investigators in question query forms asking them whether the medications in question had been administered during a particular "unspecified" time frame during the acute attack. You indicated that the majority of these queries were answered by the investigators as "no."

Therefore, we request you submit:

- a table and database showing the original CRF entries for "any rescue medication" (i.e., any medications with analgesic or anti-emetic properties ("discouraged medications") or "Non-permitted medications" which, according to the original CRF entries, were being taken at subject screening or at the time of randomization including:

- separate columns showing the updated information received in response to your queries to investigators.

    - additional columns showing the dates of subject screening, randomization, and the dates the investigators provided their responses to your queries about these medications.

- For any instances where these medications were indicated on the original CRF entries as "continuing" or being continued, we request you submit:

    - copies of the actual hospital medication records for the 5 hour period preceding and the 24 hour period following the time of administration of randomized masked (blinded) study medication. These are needed to resolve possible/apparent discrepancies between the original CRF entries and investigators' responses to the data query forms.

    - table and database showing the dates and times of administration of "any rescue medication (i.e., any medications with analgesic or anti-emetic properties ("discouraged medications") or "Non-permitted medications." "Any rescue medication" should include, but not be limited to, the list of concomitant medications provided to you by us on November 13, 2008 in an Excel spreadsheet entitled "ForbiddenMeds.xls." **The times of administration of "any rescue medication" should reflect the actual hospital source medication records for all instances where these medications were indicated as "continuing" or "being continued" on the original CRFs**.

Sponsor's Response

CSLB Response 5B1+5B2:

*Listing_**Q5b12** and -b(4)- dataset **CRLQ5b12** in CDROM subfolder Attachment 5B1+5B2 present the requested data **for subjects who received "non-permitted" medications** starting prior to start of blinded study medication and recorded by the investigator as "ongoing" on the prior/concomitant medication CRF. **In response to CSLB's queries, stop dates were obtained for Subjects --b(6)----------, and these are reflected in the listing and dataset.***

*These **queried "non-permitted" medications** include only the medications on the prohibited medication list in Appendix IVa of the SAP for the final analysis (Version 2.0 dated 26 October 2007), and they **do not comprise the additional "discouraged" medications from CBER's list of 13 November 2008, as no queries were sent with respect to these medications.** However, **CSLB has generated the requested dataset CRL_Q6BR to include the additional medications from CBER's list** (see CSLB Response 6 and CDROM subfolder Attachment 6\revised data robustness analysis).*

Thus, queries were only sent for subjects who were documented on the prior/concomitant medication CRF to have received any of the following:

- *Narcotic pain medication, and/or*
- *Anti-emetics, and/or*
- *Open-label C1-INH, and/or*
- *FFP*

*starting before the start of the attack/start of study medication and documented as "ongoing" (CMONGO = "ongoing") on the prior/concomitant medication CRF. **Copies of the individual Data Clarification Forms (DCFs) are located in CDROM subfolder Attachment 5B1+5B2.***

*The **investigator's responses to CSLB's queries** were entered into the clinical database system (-b(4)- Clinical) and are available as variable **INVCMT** in **datasets OCICMT and ADCM**. Datasets ADCM and OCICMT of the original database (safety follow-up) are located in CDROM subfolder 3_Datasets and Programs\3.2_Original database safety follow-up. Dataset ADCM is additionally located in CDROM subfolder Attachment 5A.*

CSLB Response 5B3a:

CDROM subfolder Attachment 5B3a contains copies of the actual hospital medication records/source data (including English translations of information relevant to concomitant medication) for the 28 subjects receiving any prohibited concomitant medication during the specified time period between 5 hours before and 24 hours after administration of randomized study medication.

For all subjects whose medication records/source data were compared with original CRF entries, CSLB has generated a listing that includes the information from the hospital medication records/source data, the corresponding original CRF entries, and the investigators' responses to the queries (Listing 5B3b_CM track changes database 08APR09.xls in CDROM subfolder Attachment 5B3b; also see CSLB Response 5B3b). Details on the outcomes of the source data

review are included in the Reviewer Guide to the Database (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

CSLB Response 5B3b:

As requested in CBER Comment 5B3a, the hospital medication records/source data to confirm the actual times of administration were collected from all subjects who received "any rescue medication" and "non-permitted medications" included in dataset PROHMED.xpt (i.e., the prohibited concomitant medication list for the additional robustness analysis conducted to address CBER Comment 5C) and documented as "ongoing" on the prior/concomitant medication CRF (location of PROHMED.xpt: CDROM subfolder Attachment 5B3b).

The requested table (Listing_Q5B3b_Listing_medications_according_PROHMED.xpt) showing the actual dates and times of administration of "any rescue medication" and "non-permitted medications" is located in CDROM subfolder Attachment 5B3b. The corresponding data are contained in dataset CRL_Q6BR (location: CDROM subfolder 3_Datasets and Programs\3.3_Robustness analysis and also in CDROM subfolder Attachment 6\revised data robustness analysis).

The comparison of the actual hospital medication records/source data to the corresponding original CRF entries and investigators' responses to the queries resulted in changes to the database. About 75% of these changes related to general comments concerning the availability of hospital records/source data and data management comments (see Listing 5B3b_CM track changes database 08APR09.xls in CDROM subfolder Attachment 5B3b; Note: In the revised database ADCM, the general comments are incorporated as variable TX, and the data management comments as variable DMCMT [CDROM subfolder 3_Datasets and Programs\3.3_Original analysis (revised database)\Datasets and 3_Datasets and Programs\3.4_Robustness analysis (revised database)\Datasets]).

Note: Any additional data changes implemented since the previous database closure are also included in Listing 5B3b_CM track changes database 08APR09.xls for completeness.

Reviewer Comment

Inspection of Listing Q5b12.pdf from amendment 25 reveals that a large number of the investigator query forms which stated that (discouraged/non-permitted) medications had not been used between the start of study attack or the start of study medication and 24 hours after treatment were received by the sponsor after considerable delays (i.e., up to 16 months or longer) from the date of randomized blinded administration of study medication. This calls into question whether the investigator would be able to accurately recall this information after such a significant time delay. Only for the 10 subjects listed below were the sponsor concomitant medication query forms dated within 180 days of randomization:

6007
-b(6)-
-b(6)-
-b(6)-
-b(6)-

-b(6)-
-b(6)-
-b(6)-
-b(6)-
-b(6)-

Inspection of Listing Q5b12.pdf from amendment 25 reveals that

Examples of the differences in time between randomization and the receipt of the investigator query form:

Subject ID	Date Randomized	Date Investigator Query Form Received by Sponsor	Time Difference Columns 2 & 3	Comment (Medication not used during specified window unless otherwise noted)
--b(6)--	04 Dec 2006	09 Nov 2007	11 months	From ToS
--b(6)--	07 Feb 2006	06 Mar 2007	13 months	From start of attack acc to diary
--b(6)--	28 Sep 2006	26 Oct 2007	13 months	From ToS
--b(6)--	01 Dec 2005	18 Dec 2006, 26 Feb 2007	12 months	Stopped prior to ToS
--b(6)--	26 Feb 2006	18 Dec 2006	10 months	No inv comment entered for loratidine. Only DCF received.
--b(6)--	18 June 2007	24 Oct 2007	4 months	From start of attack
--b(6)--	17 Feb 2007	26 Oct 2007	8 months	From ToS
--b(6)--	14 Aug 2005	18 Dec 2006, 21 Feb 2007	16 months	From ToS
--b(6)--		18 Dec 2006 21 Feb 2007 29 Oct 2007		From ToS
--b(6)--		18 Dec 2006, 21 Feb 2007		From ToS
--b(6)--		29 Oct 2007		From ToS

--b(6)--		**9 Nov 2007**		**From ToS**
--b(6)--		**18 Dec 2006 30 Apr 2007**		**From Start of Attack**
--b(6)--		**18 Dec 2006 26 Feb 2007**		**From Start of Attack**
--b(6)--		**18 Dec 2006 26 Feb 2007**		**From Start of Attack**
--b(6)--		**25 June 2006**		**From Start of Attack**
--b(6)--		**18 Dec 2006 26 Feb 2007**		**From Start of Attack**
--b(6)--		**18 Dec 2006 26 Feb 2007**		**From start of Attack**
--b(6)--		**20 Jun 2007**		**From Start of Attack**
--b(6)--		**18 Dec 2006 26 Feb 2007**		**From Start of Attack**
--b(6)--		**20 Jun 2007**		**From Start of Attack**
--b(6)--		**20 Jun 2007**		**From Start of Attack**
--b(6)--		**21 Jun 2007**		**From ToS**
--b(6)--		**21 Jun 2007**		**From ToS**
--b(6)--		**21 Jun 2007**		**From ToS**
--b(6)--		**26 Oct 2007**		**From ToS**
--b(6)--		**25 Oct 2007**		**From ToS**
--b(6)--		**12 Mar 2007**		**From ToS**

In cases where the hospital source records were not available or were inadequate to convincingly address whether potentially confounding concomitant medications may have been taken between -5 hours and ToS, and where the CRF box checked "ongoing" for a particular discouraged or non-permitted medication, notwithstanding the investigator's response to exclusion criterion 15 and the investigator query form response, if any, the FDA has performed various sensitivity analyses as follows:

(a) FDA assigned "poor/failure" 24 hour values for the primary efficacy endpoint for all cases in which potentially confounding concomitant medications (other than androgens prescribed to be taken on a regular basis, but not prn androgens and aspirin in the dose of 81 mg or less) were marked on the CRF as "ongoing" and where the sponsor has not submitted any medication source documents, or where the source documents and CRF data were judged ambiguous as to whether such medications were taken between -5 hours and ToSRel (Most Conservative Analysis).

(b) FDA assigned "poor/failure" 24 hour values for the primary efficacy endpoint for all cases in which potentially confounding concomitant medications (other than androgens prescribed to be taken on a regular basis, but not prn androgens and

aspirin in the dose of 81 mg or less) were marked on the CRF as "ongoing" and where provided source documents suggest a reasonable possibility that such medications may have been taken during the time window of interest (i.e., where such source documents are judged less definitive than a clear hospital record showing no such medications being taken during the time window of interest) (Intermediately Conservative Analysis).

(c) FDA accepted the statements on the investigator query form as factual if it was received by the sponsor within 180 days of the date of randomization, and the FDA analysis will accept the CRF box checked "ongoing" and assume the medication (other than androgens prescribed to be taken on a regular basis, but not prn androgens and aspirin in the dose of 81 mg or less) was administered between 5 hours prior to ToS and ToSRel if the investigator query form was received > 6 months from the date of randomization (or if other source document indicate potentially confounding medications (including, but not limited to PROHMED dataset medications) were plausibly taken during the time window of interest). Review of concomitant medications taken during -5 hours prior to randomization and ToSRel revealed that clonazepam and mirtazepine, both benzodiazepines, should have been included on the PROHMED list but were not. (Least Conservative FDAAnalysis).

I categorized, while personally masked to treatment group assignment, the subset of high dose and placebo subjects from the pivotal trial who appear in sponsor data listing Q5B3B (subjects Prohibited/discouraged concomitant medication according to PROHMED, as well as 2 additional subjects who may have taken benzodiazepines between -5 hours ant ToSRel) into those for whom a 24 hour value should or should not be imputed for analyses FDA a, b, and c above, based on masked review of source documents and selected data from data sets submitted in amendment 25. When working with datasets that contained treatment group information, I first hid the treatment group column before assessing the data. I excluded from my classification for imputation activities subjects on a list of low dose subjects provided by the FDA statistician in order to focus on the high dose vs. placebo primary endpoint analysis.

In addition, a modified sponsor analysis (R2 analysis) was performed. For the R2 analysis, imputation of a poor/failure 24 hour value for the primary endpoint was performed according to FDA analysis "c" above, except that 24 hours will not be imputed for subjects solely because they took a non-narcotic analgesic between -5 hours and ToSRel.

The above analysis algorithms were formulated without knowledge of the randomization assignments and seem reasonable in terms of what an investigator might reasonably be expected to recall/not recall after a 6 month period.

Inspection of Listing Q5B3B "Prohibited/discouraged concomitant medication according to PROHMED including classification and time between start of blinded study medication and start of concomitant medication") provides the following specific time periods in relation to ToS when such potentially confounding

medications were administered. A partial listing of consecutive subject ID numbers abstracted from this listing follows. Additional information gleaned from review of source documents (SDs) was used in constructing the -b(4)- table described below which was provided to the FDA statistician to help running the primary endpoint analyses. The table immediately below abstracts data primarily from the Q5B3B data listing.

Subject ID No.	Discouraged or Non-Permitted Medication	Time Medication Given in Relation to ToS	ToS	TTREL/ RTTRELLP	Investigator Query Response/ Comment based on Answer to Exclusion Criteria Questions 12[a], 14[b], or 15[c]	CONSISTENT ?
--b(6)--	Danazol 50 mg po prn	Start 2002, ongoing, no end date			none	
--b(6)--	Odansetron 4 mg po prn	Start prior 2004, ongoing, no end date			Excl criteria 15 = no; not used betw start of attack and 24 hours	
--b(6)--	Fexofenadine 180 mg po qd	Prior 2004, ongoing, not stop date				none
--b(6)--	Prednisone 20 mg po prn	Prior 2002, ongoing, no end date			Not used between randomiz and day 7-9 (-b(4)- finding)	
--b(6)--	Lorazepam (Ativan) 0 5 mg po prn	Prior 2003, ongoing, no end date			Excl criteria 15 = no; no tused betw start of attack and 24 hrs	
--b(6)--	Perocet (Tylox) 1 tab prn	Start prior, no end date listed, Ongoing			None	
--b(6)--	(Darvocet	Start 9 Feb			None	

	(Propacet) 1 tab prn	**2006 (Day 1), also taken days 2, 3, 5, and 9)**				
--b(6)--	**Cetirizine 10 mg po prn**	**Prior start unk, ongoing, no end date**			**Excl criteria 15 = no; not used betw ToS and 24 hrs (b(4)- finding)**	
--b(6)--	**Tylenol 500 mg prn**	**9 Nov 2006 (DAY 3)**			**None**	
--b(6)--	**Danazol 900 mg po qd**	**Ongoing**			**none**	
--b(6)--	**Danazol 400 mg po qd**	**Start prior 2003, end 20 Nov 2007**			**none**	
--b(6)--	**C1-Inaktivator IV 2x per week**	**Start 29 Oct 2007 time unk (36 days), end 30 Dec 2007**			**none**	
--b(6)--	**Tegaserod (Zelnorm) 6 mg po prn**	**Started prior 2002, ongoing, no end date**			**Excl criteria 15 = no; not used betw ToS and day 7-9 (b(4)- finding)**	
--b(6)--	**Promethazine 25 mg pr prn**	**Started prior unk date, end Nov 20005**			**none**	
--b(6)--	**Vicodin 1 tab po prn q 8 hrs**	**Started prior 20 Nov 2005 (-11 days), end 29 Nov 2005 (-2 days)**			**none**	
--b(6)--	**Hydrocodone 7.5 mg bid**	**Start 27 Feb 2006 (6+ days), 88and 29 Feb 2006**			**none**	
--b(6)--	**Loratidine prn**					**Lost diary,**

--b(6)--	**Demerol 12 mg begun 17 Feb '07, no end date**	**begun 17 Feb '07, no end date**	**Attack began 17 Feb 2007, --b(4)---------- care division record on 23 Feb 2007; Allergy evaluation dated 22 Nov 2006 states takes benadryl, Zyrtec, and steroid but dx HAE just 1 month ago., -b(4)- ER on 17 Feb '07 abd swelling states no meds, study drug administered at 8:10; relief from medication at 8:30.**	**pain resolved after 15 min, she recurred ~ 9 hrs later and went to ER., TTREL = 20 min.**	**2**	
--b(6)--	**Naproxen Na 220 mg po prn**	**Prior 1996, ongoing, no stop date**			**none**	
--b(6)--	**Fexofenadine 180 mg po qd**	**Began prior, no stop date, note from nurse that routine meds taken prior**				**no diary dispensed, abd exam normal at d/c or 24 hrs, rescue med given, compl res iby 24 hrs**
--b(6)--	**Danazol 200 mg po qd**	**1999, ongoing, no stop**			**none**	

		date				
--b(6)--	**Paracetamol x 1**	**17:30 on 17 Feb 2007 (9.5 hr)**			**None**	
--b(6)--	**Pethidine (Demerol) IV x 1**	**Begun at -12 hr 5 m on 17 Feb 2007 at 20:05**			**None**	
--b(6)--	**Hydroxyzine embonate**	**- 1 hr 15 m, acc to CRF, attack began 11:45 PM 13 Aug '05**	**14 Aug 05 at 2:35 AM**		**Narcotics, Anti-emetics not used betw. ToS and 24 hrs (SDV finding); Narcotics, Anti-emetics not used betw. Start of attack and 24 hours (Ex crit 15)**	**No, local lab opiate test positive, central lab opiate test neg, CRF reports frequent narcotic use during frequent pain episodes and does not have "x" by use of narcotic or anti/emetic meds betw start of attack enrollment**
--b(6)--	**Demerol 50 mg IV/PO prn HAE or arthritis!**	**Ongoing, 1 day after ToS**				**Not listed in Table Q5B3b**
--b(6)--	**FFP**	**Ongoing**			**Ex crit 14 No**	
--b(6)--	**Flurbiprofen**	**Ongoing, 0 days**			**None**	
--b(6)--	**Vicodin**	**Ongoing, 1 day, 3 days; 15, 16, and 17 Aug '05**			**Not used between ToS and 24 hr, ex crit 15**	

--b(6)--	**Stanozolol 50 mg po prn**	**Ongoing**			**None**	
--b(6)--	**Valsartan (ACE Inhibitor, prohibited 4 weeks prior to tx)**	**Ongoing, 4d 3hr 55min**			**None**	
--b(6)--	**Diphenhydramine 50 mg**	**Ongoing, 8 days**			**Not used betw. ToS and 24 hrs (Ex cl 15)**	
--b(6)--	**Hydroxyzine**	**Ongoing, 1 day**			**Not used betw ToS and 24 hrs (Ex cl 15)**	
--b(6)--	**Prednisone 5 mg**	**No info as to ongoing, begun -77 days**				
--b(6)--	**Plasma Protein Fraction prn**	**Ongoing**			**Not used betw ToS and 24 hrs (Ex cl 14), not used within previous 7 days**	
--b(6)--	**Tylenol prn**	**Ongoing**			**Not used betw. ToS and 24 hrs (-b(4)-finding)**	
--b(6)--	**Stanozolol 6 mg po qd**	**Ongoing**			**None**	
--b(6)--	**Ibuprofen prn**	**Ongoing**			**Not used betw ToS and 24 hrs (SDV finding)**	
--b(6)--	**Naproxen**	**Ongoing, 6 days, 7 days 23 hr**			**Med not used betw. Random. And 24 hrs (-b(4)-finding)**	
--b(6)--	**Ibuprofen**	**2 days**				
--b(6)--	**Demerol**	**Ongoing, 4 days, source doc states admitted 7**	**Source record: 8 AM on 6 Aug '05, fluctuating**	**18:30 20 Aug '05**	**Not used betw ToS and 24 hrs (15), Not used betw. Start of attack**	**No.**

		Aug and Tx with IV Demerol & adrenalin, also po Demerol 1-2x per mo	**intensity, readmitted 20 Aug**		**and ToS.**	
--b(6)--	**Danazol 50 mg**	**No info as to ongoing**				
--b(6)--	**ASA 81 mg**	**Ongoing**			**None**	
--b(6)--	**Naproxen**	**Ongoing**			**None**	
--b(6)--	**Tylenol BID**	**-5 days started, ? Ongoing**			**None**	
--b(6)--	**Danazol 200 mg qd**	**Ongoing**			**None**	**No hospital source records provided**
--b(6)--	**Hydroxyzine IM**	**6 hr 25 min**				**No hospital source records provided**
--b(6)--	**Diphenhydrmine IV prn**	**7 hr 25 min on 2 Sept at 1:25, ongoing**				**No hospital source records provided**
--b(6)--	**Diphenhydrmine po**	**Ongoing**			**Not used betw ToS and 24 hrs (15); not used betw. Start of attack aqnd ToS**	
--b(6)--	**Tylenol**	**Ongoing**			**Not used betw random and day 7-9 (-b(4)-finding)**	
--b(6)--	**Hydroxyzine po**	**Ongoing**			**Ex cl 15, Not used betw. Start of attack and ToS (-b(4) finding)**	
--b(6)--	**Hyoscyamine SL**	**Ongoing**			**Ex cl 15; Not used betw.**	

					Tos and 24 hrs (-b(4)-finding)	
--b(6)--	**Valproate**	**? Ongoing**			**None**	
--b(6)--	**Ibuprofen**	**1 day**			**None**	
--b(6)--	**Danazol 100 mg BID**	**? Ongoing**			**None**	
--b(6)--	**Diphenhydramine PO prn**	**Ongoing**			**Ex cl 15; Not used between start of attack and ToS**	
--b(6)--	**Ibuprofen**	**1 day, ongoing**			**None**	
--b(6)--	**Danazol 200 mg qd**	**Ongoing**			**None**	
--b(6)--	**Promethazine**	**Ongoing, 9 hr 47 min, 18 through 19 April '06**			**Ex cl 15; Not used betw. Start of attack and ToS**	
--b(6)--	**Darvocet**	**Ongoing**			**Ex cr 15; Not used betw. Start of attack and ToS**	
--b(6)--	**Danazol 300 mg BID**	**Ongoing**			**None**	
--b(6)--	**Promethazine IV**	**5 hr 13 min**			**None**	
--b(6)--	**Fentanyl IV**	**5 hr 13 min**			**None**	
--b(6)--	**Ibuprofen prn**	**? Ongoing**			**None**	
--b(6)--	**Oxandrolone 5 mg po prn**	**? Ongoing**			**None**	**No source documents provided by sponsor**
--b(6)--	**Odansetron IV**	**4 hr 25 min, 1 day**			**None**	**No source documents provided by sponsor**
--b(6)--	**Morphine IV**	**4 hr 5 min**			**None**	
--b(6)--	**Demerol PO**	**1 day**			**None**	
--b(6)--	**Fexofenadine**	**Ongoing**			**Ex cr 15; not used betw. Start of attack and ToS**	
--b(6)--	**Tylenol 1 g prn**	**-1 day,**			**Not used**	

		ongoing			**between ToS and day 7-9 (-b(4)-finding)**	
--b(6)--	**Danazol 200 mg prn**	**? Ongoing**			**None**	
--b(6)--	**Promethazone 25 mg po**	**Ongoing**			**Ex cl 15: Not used betw. Start of attack and ToS.**	
--b(6)--	**Oxandrolone 17.5 mg po qd**	**? Ongoing**			**None**	**No source records provided by sponsor**
--b(6)--	**Nyquil 7.5 mL po (antihistamine)**	**1 day**			**None**	**No source records provided by sponsor**
--b(6)--	**Alprazolam 0.5 mg po qd**	**? Ongoing**				**No source records provided by sponsor**
--b(6)--	**Tylenol Allergy Complete (includes antihistamine)**	**Ongoing**			**Not used between Tos and day 7-9 -b(4)- finding)**	**No source records provided by sponsor**
--b(6)--	**Ibuprofen 400 mg**	**4 days**				**No source records provided by sponsor**
--b(6)--	**Tylenol**	**5 days**				**No source records provided by sponsor**
--b(6)--	**Morphine Elixir 20 mg prn po**	**Ongoing**			**Not used betw ToS and day 7-9 (-b(4)-finding; Ex cr 15; Not used between start of attack and ToS.**	**No source records provided by sponsor**
--b(6)--	**Fentanyl patch 25 mcg**	**? Ongoing, - 945 days**			**None**	**No source records provided by sponsor**
--b(6)--	**Stanozolol 4 mg**	**Ongoing, -**			**None**	

	QD	**56 days**				
--b(6)--	**Alka-Selzer Plus cold 2 prn**	**Ongoing, - 19 days**			**None**	
--b(6)--	**Promethazine po prn (Phenergan)**	**6.25 mg ? Ongoing Ongoing crossed out but not dated;, ended 23 June 2006**	**11:54 AM 25 Jun 06**		**None**	**Records provided by sponsor do not show times or dates given**
--b(6)--	**Alprazolam 0.5 mg po prn (Xanax)**	**Ongoing, - 5 days**			**Ex cl 15; Not given between start of attack and ToS**	**Records provided by sponsor do not show times or dates given**
--b(6)--	**Vicodin prn (hydrocodone)**	**Ongoing crossed out but not dated;-2 days, ? Ongoing, stop date 23 June 06**			**Ex cl 15; Not taken betw. Start of attack and ToS**	**Records provided by sponsor do not show times or dates given**
--b(6)--	**Darvocet prn**	**Ongoing crossed out but not dated; 02 days, stopped 23 June 2006**			**None**	**Records provided by sponsor do not show times or dates given**
--b(6)--	**Diphenhydramine po**	**Days 1, 5**			**Ex cr 15; not used between start of attack and ToSRel**	
--b(6)--	**Ibuprofen**	**Ongoing**			**Not used between ToS and 24 hours (-b(4) finding)**	
--b(6)--	**Danazol 100 mg q 7 days**	**Ongoing, - 27 days**			**None.**	
--b(6)--	**Diphenhydramine po**	**-233 days until 11 Sep 2006**				

--b(6)--	**Diazepam po**	**3 days**			**None**	
--b(6)--	**Naproxen**	**Ongoing, days 4, 8**			**Not used betw. Start of attack and day 7-9 (b(4) finding)**	
--b(6)--	**Stanozolol 2 mg po qd**	**Ongoing**			**None**	
--b(6)--	**Stanozolol 1 mg po prn**	**Day 1**			**None, dose lowered and changed to prn**	
--b(6)--	**Fexofenadine**	**Ongoing**			**Ex cr 15; not used betw. ToS and 24 hr (b(4) finding)**	
--b(6)--	**Tylenol**	**Ongoing, day 7**				
--b(6)--	**Ibuprofen**	**Ongoing, day 7**				
--b(6)--	**Phenergan VC W/Codeine Elixir**	**-2475, End 8 Oct 2006**				
--b(6)--	**Danazol 200 mg prn**	**Ongoing**			**Not used betw. 5 hr prior to ToS and complete resolution**	
--b(6)--	**Vicks Formula 44M prn**	**4 days; end 13 Nov 2006**				
--b(6)--	**Danazol 200 mg po qd**	**-170 days; end 6 Nov 2006**			**none**	
--b(6)--	**Promethazine HCl (Phenergan)**	**15 mg prn, Feb 2006, ongoing**			**Not used bewt – 5 hrs and 24 hrs (-b(4)-finding), Exclusion Criteria Q 15 = no**	
--b(6)--	**Azelastine HCl;**	**274 mg IN BID, start 10 Apr 2006, ongoing**			**Not used betw start of attack & TTREL, Ex criteria 15 = no**	
--b(6)--	**Diphenhydramine**	**25 mg BID**			**none**	

		prn 11 Dec '06 started, ended 12 Dec 2006, taken 2 days in relation to ToS				
--b(6)--	**Theraflu**	**Prn 12 thru 14 Dec '06, 3 days in relation to ToS**			**none**	
--b(6)--	**Ibuprofen**	**400 mg prn, 12 Dec thru 17 Dec '06, 3 days in relation to ToS**			**none**	
--b(6)--	**Naproxen prn**	**Start 12 Dec 06 end 13 Dec 06, 3 days**			**none**	
--b(6)--	**Stanozolol 2 mg po qd**	**ongoing**			**none**	
--b(6)--	**Tylenol 1 g prn**	**ongoing**			**Not used between random and day 7-9 (b(4) find)**	
--b(6)--	**Danazol 400 mg po qd**	**Ongoing**			**None**	
--b(6)--	**Oxandrolone 2.5 mg po qd**	**Ongoing**			**none**	
--b(6)--	**Cogentin (benzatropine) 1 mg po qd**	**Ongoing**			**none**	
--b(6)--	**Diphenhydramine 25 mg po prn**	**Ongoing**			**Excl crit 15 = no; not used betw start of attack and ToS (-b(4)-)**	
--b(6)--	**Tylenol 500 mg**	**Ongoing**			**none**	

	BID	**starting 12 April 2007 6 days**				
--b(6)--	**Prednisone 5 mg po qd**	**Started May 2006, ongoing**			**none**	
--b(6)--	**Danazol 200 mg po prn**	**Start Feb 2007 (-91 days), ongoing**			**none**	
--b(6)--	**Loratadine 10 mg po prn**	**Start – 10 days on 14 Apr '07, end 5 days, ongoing**			**none**	
--b(6)--	**Tylenol 500 mg po prn**	**4 May '07 1 day**			**none**	
--b(6)--	**Ibuprofen 200 mg po prn**	**7 May '07, start time unk, end 7 May '07, 3 days**			**none**	
--b(6)--	**Desloratadine**	**5 mg po qd start 2006, end 15 sept 2007**			**none**	
--b(6)--	**Danazol 200 mg po qod**	**Ongoing, -156 days**			**none**	
--b(6)--	**Danazol 100 mg po bid**	**Start 1991, end Aug 2006**			**none**	
--b(6)--	**Promethazine unk/iv/prn**	**start 30 Mar 2006, time unknown, end 02 Apr 2006, 0 days**			**`none**	
--b(6)--	**Demerol 50 mg IV**	**30 Mar '06 at 13:32 (0 hr 54 min), & 18:02 (5 hr 24 min)**			**none**	
--b(6)--	**Vicodin (hydrocodone) 7.5 mg po prn**	**Start 02 Apr 2006 time unk**				

		(3 days), ongoing				
--b(6)--	**Clonazepam 1 mg po bid (not listed in table but listed in furnished ZLB document0**	**Start 1996, no stop date**				
--b(6)--	**Perchlorperazine 10 mg prn**	**Start -890 days, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Promethazine 25 mg q h prn**	**Start -2716 days, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Diphenhydramine 25 mg po prn**	**Start -1620 days, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Hydroxyzine 10 mg po prn**	**Start 2005, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**C1-Inaktivator IV**	**12 June 2006 at 15:29 (3 days 4 hr 57 min) & 16 June 2006 at 18:59 (7+ days)**			**none**	
--b(6)--	**Perocet QID [prn according to table but prn not listed on handwritten ZLB document]**	**2005 (-524 days), ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Vicodin prn**	**Start 12 June 2006 at 17:43 (3 days 7 hr 11 m) ongoing**			**Not used between randomiz and day 7-9 (-b(4)-find)**	
--b(6)--	**Aminocaproic acid 2 g po qid**	**4 Apr ’06 (-197 days),**			**none**	

		ongoing				
--b(6)--	**Dicycloverine HCl 20 mg po prn**	**Start 2001, ongoing**			**Not used between randomiz and day 7-9 (b(4)-find)**	
--b(6)--	**Danazol 100 mg po prn**	**2004, ongoing**				
--b(6)--	**Promethazine 25 mg prn**	**2001, ogoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Ketorolac (Toradol) 10 mg po prn**	**2001, ongoing**			**Not used between randomiz and day 7-9 (b(4)-find)**	
--b(6)--	**Dolasetron IV prn**	**2001, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Dicloverine 10 mg prn**	**Start 27 Sep 2006 (-152 days), ongoing**			**Excl crit 15 = no,Not used between randomiz and day 7-9 (b(4)-find)**	
--b(6)--	**Morphine 2 mg IV prn**	**2001, ongoing**			**Excl crit 15 = no, not used betw ToS and 24 hrs**	
--b(6)--	**Loratadine 10 mg po prn**	**Mar 2006 (- 178 days), ongoing**			**Excl crit 15 = no, not used betw ToS and TTRel**	
--b(6)--	**C1 INAKTIVATOR iv**	**19 Mar 2007 (4 days 1 hr 45 min)**			**none**	
--b(6)--	**Stanozolol 2 mg po prn**	**12 Jan 2007 (-209 days), ongoing**			**Not used between -5 hr & complete resolution**	
--b(6)--	**Promehazine 25 mg IV x 1**	**9 Aug 2007 23:54 (3 hr 4 min)**			**None**	

--b(6)--	**Ketorolac (Toradol) 30 mg IV x 1**	**9 Aug 2007 (3 hr 4 min)**			**none**	
--b(6)--	**Tramadol 50 mg po prn**	**2004, ? ongoing**			**none**	
--b(6)--	**Danazol 400 mg po qd**	**2004, ongoing**				
--b(6)--	**C1-Inaktivator IV**	**20 Sep 2006 at 18:00(-3 days 1 hr, 10 min), 26 Sep 2006 at 16:00 & 29 Sep 2006 22:15 (2 d 20 hr 50 min & 6 days 3 hr 5m)**			**none**	
--b(6)--	**ASA 500 mg prn**	**24 Sep 2006 1:00 (5 hr 50 min)**			**none**	
--b(6)--	**Tylenol 325 mg prn**	**Start 5 Oct 2006 (1 day), 3 days**			**none**	
--b(6)--	**Prochlorperazine unk iv x 1**	**1 May 2006 unk time (4 days)**			**none**	
--b(6)--	**C1-Inaktivator (Berinert) IV x 1**	**21 May 2006 time unk!, (4 days)**			**none**	
--b(6)--	**Tylenol 500 mg po prn**	**1999, ongoing**			**Not used betw random and da 7-9 (-b(4)-find)**	
--b(6)--	**Demerol unk iv x 1**	**21 May 2006 (4 days)**			**none**	
--b(6)--	**C1-Inaktivator**	**29 Dec 2006 (9 DAYS)**			**NONE**	**No source documents provided**

--b(6)--	**Danazol 450 mg po qd**	**2005, ongoing**				
--b(6)--	**Zelnorm (tegaserod) 2 mg po bid**	**Jan 2007 (-66 days), ongoing**			**none**	
--b(6)--	**Ibuprofen 800 mg TID**	**Start 9 Mar 2007 (1 day)**			**none**	
--b(6)--	**Celecoxib 100 mg x 1**	**Start unk, end 29 June 2007**			**none**	
--b(6)--	**C1-Inaktivator IV**	**27 Sept 2007 (7+ days)**			**none**	
--b(6)--	**Ocycocet (Roxicet) po prn**	**Start prior, ongoing**			**Not used between ToS and TTRel**	
--b(6)--	**Fioricet w codeine po q 4 hr prn**	**Start prior unk, ongoing**			**Excl crit 15 = no, Not used betw -5 hr and 24 hrs (-b(4)-finding)**	
--b(6)--	**Danazol 200 mg po tid**	**Start 2002, ongoing**			**none**	
--b(6)--	**Diphenhydramine 50 mg po prn**	**2002, ongoing**			**Excl crit 15 = no, Not used betw -5 hr and 24 hrs (-b(4)-finding)**	
--b(6)--	**Oxycodone (Oxycontin) 10 mg po prn**	**Start 2003, ongoing**			**Excl crit 15 = no, Not used betw -5 hr and 24 hrs**	
--b(6)--	**Oxycodone 10 mg po qd**	**Start 5 July 2006 (7 days), end 6 July 2006**				
--b(6)--	**Tranexamic Acid 500 mg po x 3 qd**	**Start 6 Feb 2006 (-146 days), ongoing, no stop date**			**none**	
--b(6)--	**Tranexamic Acid 500 mg po x 2 qd**	**Start 6 Apr 2006**			**none**	

		(-117 days), ongoing, no stop date				
--b(6)--	**Danazol 400 mg po prn**	**Start 2005 (-382 days), ongoing**			**None**	
--b(6)--	**Stanozolol 2 mg po qd**	**Start 2005, ongoing, no stop date**			**none**	
--b(6)--	**Co-Advil 200 mg po qd**	**Start Dec 2006 (-3 days), stop 5 Dec 2006**			**None**	
--b(6)--	**Tranexamic Acid 500 mg po bid**	**Start 2005 (-7004 days), ongoing, no stop date**			**None**	
--b(6)--	**Danazol 200 mg bid**	**Start 17 April 2007, time unk, stop 17 Apr 2007 (0 days)**			**Med not used between -5 hrs and ToS (b(4) finding)**	
--b(6)--	**Drotaverine (Nospa) 40 mg x 1**	**Start prior 17 Apr 2007, time unk, stop 17 Apr 2007 (0 days)**			**Excl crit 15 = no; not used betw -5 hrs and ToS**	
--b(6)--	**Metamazole Na (Pyralginum) 5 mL IV x 1**	**Start 17 Apr 2007 (0 days), stop same date, no answer to "Started prior to study?"**			**None**	

--b(6)--	**Scorbolamid (analgesic/ antipyretic) 1 tab 3x1**	**Start 20 Apr 2007 (day 3 and 59 min)**			**None**	
--b(6)--	**ASA plus C 500 mg x 1**	**21 Apr 2007 (4 days +)**			**None**	
--b(6)--	**ASA 100 mg po qd**	**Start 1991, ongoing except on 21 Oct 2006 (day 0)**			**None**	
--b(6)--	**C1-Inaktivator (Berinert P) 500 U IV x 1**	**09 Aug 2007 at 8:15 AM (5+ days)**			**None**	
--b(6)--	**Tranexamic Acid 500 mg po bid**	**2002, ongoing, no end date**			**None**	
--b(6)--	**Enalapril**	**Nov 2006 (-176 days) through 10 Jan 2007**			**None**	
--b(6)--	**Danazol 200 mg qd**	**Start May 2006)-377 days, end 29 Apr 2007**			**None**	
--b(6)--	**Danazol 600 mg po x 1**	**03 Mar 2006 at 20:00 (1 day 19 hr 15 min)**			**None**	
--b(6)--	**Danazol 200 mg po x 1**	**4 March 2006 (2 days +)**			**None**	
--b(6)--	**Desloratadine**	**12 Jan 2006 at 10:30 AM (- 6 hr 26 min), end same date**			**none**	
--b(6)--	**C1-Inaktivator IV x 1**	**05 July 2007 at**			**None**	

		19:20 (13 days +)				
--b(6)--	**Hydrocortisone Na succinate IV x 1**	**17 June 2007 at 9:30 (61 days+)**			**None**	
--b(6)--	**Clemastine 1 mg IV x 1**	**17 June 2007 (day 61)**			**None**	
--b(6)--	**Diclofenac Na pr**	**20 apr at 8:30 (3 days 7 hr 55 min), 21 Mar and 23 Mary 2007**			**None**	
--b(6)--	**Tranexamic Acid 250 mg po BID**	**Start 2002, stop 27 Oct 2006**			**None**	
--b(6)--	**Tranexamic Acid 500 mg po BID**	**27 Oct 2006 (7 days), ongoing**			**None**	
--b(6)--	**Loratadine 10 mg po**	**Start 2001, ongoing**			**Excl criteria 15 = no; not used betw ToS and time of complete resolution**	
--b(6)--	**Tranexamic Acid 500 mg TID**	**Prior, ongoing**			**Not used in this dosage during study**	
--b(6)--	**Tranexamic Acid 250 mg BID**	**Start 1996, ongoing**			**Dosage not changed from start of attack to complete resolution**	
--b(6)--	**Danazol 100 mg po qd**	**Prior 2006, ongoing, no stop date**			**None**	
--b(6)--	**Tylenol 1 g x 1**	**11 April 2007 time unk (0 days), "Started**			**None**	

		prior to study?" left blank				
--b(6)--	**Metamizole Na (Optalgin) 500 mg po**	**26 Jul 2007 at 8:0 (7 das +)**			**None**	
--b(6)--	**Tranexamic acid 1 g po qd**	**26 Jul 2007 (7 days +)**			**None**	
--b(6)--	**Promethazine HCl 12.5 mg IV qd (not prn)**	**10 Sep 2007 at 13:25 (1 hr 30 min), stop same day**			**None**	
--b(6)--	**Promethazine HCl 6 mg x 1**	**13 Sep 2007 (3 days)**			**None**	
--b(6)--	**Promethazine HCl 12.5 mg x 1**	**13 Sep 2007 (5 days)**			**None**	
--b(6)--	**Promethazine HCl 6 mg x 1**	**15 Sep 2007 (7 days)**			**None**	
--b(6)--	**C1-Inaktivator 500 U IV qd**	**Start 13 Sept 2007, time unk (3 days), stop same day**			**None**	
--b(6)--	**Oxycodone 4 mg x 1**	**11 Sept 2007, time not listed (1 day)**			**None**	
--b(6)--	**Oxycodone 2 mg x 1**	**13 Sept 2007, time not listed (3 days)**			**None**	
--b(6)--	**Oxycodone 3 mg x 1**	**17 Sept 2007, time not listed (7 days)**			**None**	
--b(6)--	**Ibuprofen 200 mg po prn**	**2007 prior, ongoing, no stop date**			**Not used between randomization and day 7-9**	

					b(4) finding)	
--b(6)--	**Tranexamic Acid 2 g po qd**	**Start 2000, stop 17 Sept 2007, Restart 21 Sept 2007 (4 days), ongoing**			**Not used from randomization and day 7-9 b(4) finding)**	
--b(6)--	**Ketorolac 10 mg po**	**Started prior on 13 Aug 2007 at 8:00 (-1 day 9 hr 49 min, stop same day. Restarted 15 Aug 2007 at 17:00 (1 day 0 hr 12 min), stop 16 Aug 2007**			**None**	
--b(6)--	**Ibuprofen 400 mg po qd**	**Start 13 Sept 2007 (2 days), end 14 Sept 2007**			**none**	
Subject ID No.	**Discouraged or Non-Permitted Medication**	**Time Medication Given in Relation to ToS**	**TTREL**	**RTTRELLP**	**Investigator Query Response/ Comment based on Answer to Exclusion Criteria Questions 12[a], 14[b], or 15[c]**	**C O N S I S T E N T ?**

[a]Exclusion Criterion 12 "Treatment with any C1-INH concentrate or any other drugs appropriate for the treatment of acute angioedema within 7 days before start of study treatment on Day 1"
[b]Exclusion Criterion 14 "Treatment with fresh frozen plasma or native plasma within 7 days before start of study treatment or Day 1"
[c]Exclusion Criterion 15 "Narcotic pain medication and/or anti-emetics between start of attack and administration of study medication"

Almost None of the self-described "source documents" provided in the amendment 25 response to our CR letter request for actual hospital medication records bears the name of the hospital. Rather, most of them bear the title "ZLB Behring CE1145-3001 Randomization / Enrollment Source Documentation." For concomitant medications, the examined sheets do not have a space in which explicitly to write the date and time of administration of medications. This is especially problematic for "PRN" medications. Most of the classes of "discouraged" and "non-permitted" medications were prescribed PRN. The submitted SDs present some difficulties to fully validate the primary endpoint for subjects for whom such medications were listed as "ongoing," notwithstanding the investigators'' claim made many months later in response to sponsor query that no such medications were taken during the period of interest. For this reason FDA performed 2 additional robustness analyses, to take into account various possible interpretations of SDs. For the purposes of this review, judgments were made based on review of each source document submitted concerning the likelihood that non-permitted medications or medications specified by the protocol to result in a poor/failure value of 24 hours for the primary endpoint for which the investigator had marked the medication(s) on the CRF as "Ongoing" may have been taken during the period of interest, i.e., from 5 hours prior to randomization to ToSRel. The results of my review of the source documents were entered into a -b(4)- dataset entitled Berinert-Imputation-Concom-Meds-X-Rescue. This data set relies primarily on my review of the submitted concomitant medication source documents

Below is a printout of selected fields from the JMP dataset entitled Berinert-Imputation-Concom-Meds-X-Rescue. The number "1" following the subject ID number indicates that from source document review of concomitant medications (but not taking into account use of blinded study rescue medication), this reviewer concluded that a 24 hour value should be imputed for the primary endpoint. A value of "2" following the subject ID number indicates that from source document review of concomitant medications (but not taking into account use of blinded study rescue medication), this reviewer concluded that a 24 hour value should NOT be imputed for the primary endpoint. Subjects without imputation ratings were low dose Berinert randomized subects.

Subject ID	Impute 24 hr?	Reason for Imputation/Lack of Imputation
--b(6)--	1	prn androgens and Amicar without statement these were not taken after attack onset and opoids pos by local lab
--b(6)--	1	Submitted source records incomplete and do not address medication during period -5 hours to ToS
--b(6)-	1	Danazol dose increased from 400 mg to 800 mg QD
--b(6)-	2	C1-Inhibitor concomitant med started > 1 month after randomization
--b(6)-	2	oxandrolone 2.5 mg po qd since 2004 and Paxil (paroxitine) 20 mg po qd since 2003. No medication records covering the period -5 hours to ToS were submitted.

--b(6)- 1 Tylenol PM 2 tabsbs po x 1 on 15 Jan 2006 at 22:30, no source doc covers - 5 hours to ToS, no stop date on Zelnorm
--b(6)- 1 Promethazine q 8 hrs prn no end date crossed out but undated and not initialed.
--b(6)- 2 Statement by investigator in response to query dated 21 Jan 2009 states no protocol prohibited meds taken -5 hours to 24 hours.
--b(6)- 1 anti-histamine without stop date or sponsor comment
--b(6)- 2 No evidence of change in androgen dose
--b(6)- 1 Zyrtec taken from age 2 through after trial, no times given in source documents.
--b(6)- 1 mirtazepine in SD but not coded into database.
--b(6)- 1 Hydroxyzine taken -1.25 hrs, Flurbiprofen taken day 0, positive opiate and hydrocodone test local lab by -b(4)-
--b(6)- 2 No meds taken 4 days prior to attack
--b(6)- 1 Advil taken at 20:30, ToS = 19 Aug 2005 at 18:00, ToS 20 Aug 2005 at 18:30, rescue medication given, ToSRel 23:30 (5 hrs)
--b(6)- .
--b(6)- 2 No meds taken at home day of attack
--b(6)- 2 At 2 hours 12 min "00:25 – Vistaril 50 mg IM administered L hip for very severe retching, gagging, and some vomiting." Three hours after study medication sheet states "Patient sleepy from Vistaril, but HA continues…Demerol 50 mg IM administered 01:21…01:25 having heaves again – Benadryl 12.5 mg IV given 01:33.
--b(6)- 2 . SD with space for randomization number states "0 nothing new since screening" under current and previous concomitant medications.
--b(6)- 1 No submitted SD addresses whether meds taken from -5 hours through ToS.
--b(6)- 1 No SD address whether meds taken -5 hours to ToS.
--b(6)- .
--b(6)- 1 Darvocet prn start date 2002, ongoing, with stop date 27 Apr 2006 (stop date day 9)
--b(6)- .
--b(6)- .
--b(6)- 2 Oxandrolone prn and marked "?Ongoing" in table Q5B3b
--b(6)- 2 Tylenol prn start date 9 Oct 2005 with no time or stop date, but note states no meds taken prior to attack /within 4 [circle superscript] post dose" .
--b(6)- 2 Note dated ~ 1 month after ToS states no anti-emetics taken or other changes to meds prior to attack.
--b(6)- .
--b(6)- .
--b(6)- 2 Acamprosate is for traeting EtOH addiction
--b(6)- 2 Medent DM 2 BID 14 April through 19 April 2006, ToS was
--b(6)- 1 No SD addresses -5 hrs through ToS ,See note re Xanax.
--b(6)- 1 Ibuprofen ongoing, Pepcid AC ongoing. No SD addresses period - 5 hrs to ToS
--b(6)- 2 No meds taken from onset of attack, which was 5 hrs 1 min prior to ToS
--b(6)- 1 Allegra prn from 2001, ongoing, Epipen prn from 2000, ongoing, no stop dates

--b(6)- 2 prn androgen "Ongoing," but SD states no current meds taken stmt on SD, no danazol from -5 hours to complete resolution
--b(6)- 2 No phergan taken since early Feb according to undated Screening/Enrollment sheet; no SD addresses -5 hours through attack resolution.
--b(6)- 2 "Subject denies taking any prohibitive medication from beginning of attack and to be discouraged during the first four-hours."
--b(6)- .
--b(6)- 2 Subject confirms not having taken any prohibited meds since beginning/onset of attack (to include narcotic pain med or anti-emetics)" in undated unsigned note on Randomization Visit SD
--b(6)- .
--b(6)- 2 Dose androgen not changed until after study period
--b(6)- 1 Cogentin (benzatropine) QD "Ongoing", no investigator query reply among SD, but Query reply in DB, time of administration not stated
--b(6)- .
--b(6)- 1 prn androgen ongoing, no sponsor comment
--b(6)- 1 no medication source documents submitted
--b(6)- 1 no medication source documents submitted
--b(6)- 1 No record of whether meds taken between - 5 hours and ToSRel
--b(6)- 2 No evidence of Danazol dose change
--b(6)- .
--b(6)- 1 Oxycodone 529 ng/mL on entry by -b(4)-, not listed as concomitant med, Percocet Rxed QID since 1999 with no stop time
--b(6)- 2 No meds taken day of randomization per note
--b(6)- 2 Ambien taken daily from prior to attack with no stop date, continuing.
--b(6)- 1 prn androgen ongoing, no sponsor comment, no info as to whether Ketorolac taken between start of attack and ToS
--b(6)- .
--b(6)- 1 No stop date for prn Stanozolol, Zyrtec prn, Protonix or Clonazepam with no times of administration given
--b(6)- 1 Tramadol 50 mg po prn, ongoing, no sponsor comment.
--b(6)- 1 No meds taken at home day of attack, but rescue medicine given after no change in symptoms at 4 hrs
--b(6)- .
--b(6)- 2 C1-INH last taken ~ 2 week prior to randomization visit, no meds "taken over the last."
--b(6)- .
--b(6)- 2 but CRF states C1 Inaktivator taken on day 9, so I will not impute failure
--b(6)- .
--b(6)- 1 rescue medication given before ToSRel (TtRel 5.9 hrs), no data query form
--b(6)- 1 Ocycocet (Roxifef) po prn no info if used between attack onset and ToS, medication records missing from source docs
--b(6)- .
--b(6)- 2 no evidence dose changed, rescue medication given

--b(6)- 2 no evidence dose changed
--b(6)- 2 prn androgen ongoing, no sponsor commenta, but source docs clear that Danazol not taken from -5 hr to 24 hrs.
--b(6)- 2 Stanozolol 2 mg/day dose not changed
--b(6)- 1 (ibuprofen +prenolozfladyne) administered on day of randomization 6 Dec 2006 at 21:50.
--b(6)- 1 Danazol 200 mg and NoSpa taken at home day of attack. Danazol used prn.
--b(6)- 2 ASA 100 mg probably not taken, but investigator states it is very difficult to be sure
--b(6)- 2
--b(6)- .
--b(6)- 2 no evidence dose changed, failure not imputed despite lack of source medication records
--b(6)- 2 no evidence dose changed, failure not imputed despite lack of source medication records
--b(6)- 1 no medication source documents submitted, no sponsor comment
--b(6)- 2 no medication source documents submitted, but CRF states C1 Inaktivator taken on days 13+, so I will not impute failure
--b(6)- 2 no medication source documents submitted
--b(6)- 2 Dose increase on day 7

--b(6)-- 1 Loratidine 10 mg according to data listing, no concomitant med list in source documents addresses whether taken from -5 hrs through ToS.
--b(6)- 2 no evidence dose changed, failure not imputed
--b(6)- 1 Tylenol 1 g x 1 day 0, time not noted, no sponsor comment
--b(6)- 1 Promethazine 12.5 mg IV QD, given at 1:45 hours after ToS, oxycodone on day 1 with time unk
, no source documents submitted
--b(6)- .
--b(6)- .
--b(6)- 2 Ibuprofen 400 mg qd begun on day 2, no medication source documents submitted

Neither actual hospital medication records nor self-described [ZLB Behring] "source documents" were provided in answer to FDA request 5B3a (Attachment 5B32_Original Medical Records folder) for several subjects who are listed in the above Table Q5B3b as having received "any rescue medication" (prohibited or discouraged medications that result in a "poor/failure" imputation for TTREL+ for the primary endpoint if taken during the time period of interest. Many of these subjects, however, began the otherwise potentially confounding medication only after ToS, in which case a 24 hour value for the primary endpoint would not be imputed on this basis.

Selected data abstracted from submitted source documents for individual subjects is given in Review Appendix 1.

- We request you re-analyze the study primary endpoint, taking into account "any rescue medication," including both narcotic and non-narcotic analgesics, anti-emetics, and all "Non-permitted" medications. The use of "any rescue medication" may otherwise confound the interpretation of the primary endpoint.

Sponsor's Response

CSLB Response 5C:

CSLB considers this additional requested analysis to be an exploratory robustness analysis of the primary endpoint. As stated in the Cover Letter and in CSLB Responses 5A and 10, CSLB's and outside consultants' position is that non-narcotic pain medications are ineffective for the treatment of acute HAE attacks and do not confound the interpretation of the primary endpoint. Consequently, these medications were not excluded/prohibited in the study protocol.

Result of the Additional Robustness Analysis

The additional robustness analysis conducted to address CBER Comment 5C clearly confirms the result of the original analysis of the primary endpoint, with a p-value of 0.014 in the primary Wilcoxon test in favor of the Berinert 20 U/kg group compared to placebo (see Table 11.17.1 in Tables_Q5c_robustness in CDROM subfolder Attachment 5C). However, the sensitivity of this additional robustness analysis decreased by imputing an additional 18.5% of the overall ITT study population to a poor/failure outcome (i.e., in addition to the 27.4% of the original analysis).

The complete dataset for the additional robustness analysis as well as the letters from the outside consultants are located in CDROM subfolder Attachment 5C (Tables_Q5c_robustness, Figures ageffkm_new_original and ageffkm_new_robustness; letters from consultants: statement --b(4)--, statement -b(4)-, statement -b(4)-).

Reviewer Comment

The sponsor has presented no data to substantiate its position that non-narcotic analgesics have no effect whatsoever on the intensity of any HAE attack symptom. In the absence of such actual data, the conservative approach is to impute a "poor/failure" outcome of 24 hours for subjects who were documented to have received such medications between 5 hours prior to ToS and ToSRel. Thus, FDA will emphasize what the sponsor terms in amendment 25 the "robustness analysis," in which non-narcotic analgesics are added to the list of medications that, if taken between hour -5 and ToSRel, result in imputation of a "poor/failure" value of 24 hours for the primary endpoint.

Inspection of the original SAP version 1.0 dated 5 March 2006 (pp 15-16) does provide one additional detail beyond what is in the protocol as to how analgesics, anti-emetics (or open-label C1-INH, or other medications non-permitted according to the protocol) would be handled in the primary analysis of the primary endpoint: It states that a 24 hour value will be imputed for TtRel+ if "the subject received analgesics/anti-emetics (*as listed in the CRF*) [emphasis added] before ToSRel was reached." However, the sponsor states in amendment 25 that they never added the promised list of analgesics and anti-emetics to the CRF; rather the sponsor states they sent the list separately to the investigators. This list was, unfortunately, never submitted to the IND so FDA never had an opportunity to comment on it. The list was further modified as the trial progressed and was included in the final version 2.0 SAP that was dated 1 week before the study was unblinded. This final SAP was never submitted to the IND, as noted by the sponsor below. Note that neither the original SAP nor the protocol actually stated that use prior to ToSRel of obviously confounding medications other than analgesics or anti-emetics (or any of the other medications "not permitted" by the protocol), such as open-label C1-Esterase Inhibitor would result in imputation of a (24 hour) poor/failure value for TtRel+. Both SAP version 2.0 and the FDA primary endpoint analyses address this deficiency, however.

Potentially confounding medications are mentioned also in the context of robustness analyses of the primary endpoint (SAP version 1.0 pp 39-40).

Of interest are the rules contained in SAP version 1.0 for determine ToSRel when a subject is asleep during 1 or more key primary endpoint per-protocol assessment times. These rules allowed the value of ToSRel to be the planned assessment time when the subject was asleep if the subject answered yes to the primary endpoint question at the next assessment time after he/she awakened. Additional rules came into play for the situation in which a subject answered a single primary endpoint question affirmatively, then fell asleep for one or more subsequent assessments (or the data were otherwise missing), and then answered the endpoint question affirmatively upon awakening. A flow diagram describing an algorithm corresponding to these rules (not in the protocol) is contained in the "Reviewer Guide to the Database" on p 14.

- We note that a number of subjects received tranexamic acid, plasma protein concentrate, and attenuated androgens during the study, according to the original concomitant medications database. However, as noted above, the original ADCM database has missing values for variable "TONALG" ("Date/Time of first analgesic after start of first administration in the respective time window") for a majority of the concomitant medications having analgesic or anti-emetic properties or that were among the list of medications "Non-permitted" by the protocol. During the teleconference held on November 12, 2008 with representatives of your firm and Drs. Wang and Pierce and Ms. Valencia of this Office, your representative indicated that you did, in fact, impute a "poor/failure" outcome of 24 hours for subjects who received any of the 6 classes of medications "Non-permitted" by the protocol, including tranexamic acid, etc.

However, inspection of Appendix IVb: "Impact of Concomitant Medications and Rescue medication on PP- and sub-population definition and on primary efficacy variable" suggests that the administration of androgens, "transexamic" [sic] acid, "aminocarproic" [sic] acid and "Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis [other than FFP]: was ***not*** taken into account in the calculation of the key variable, "$TtRel^{+}$" (also variously called "TTRELP" and "TTREL+"), which was defined, according to your DEFINE.pdf document, as "Time to relief of symptoms with p/f ass [poor/failure assessment]." and "TTRELP = TTREL with poor/failure assessment: TTRELP = 24 if use of analgesics or rescue medication before start of relief nor no relief was reached otherwise TTRELP – TTREL." Please clarify.

Additional details and problems concerning your data and submissions that have impeded our validation of your efficacy analyses are listed in the Appendix to this letter.

Sponsor's Response

CSLB Response 5D:

For clarification of missing values of the variable TOANALG, please refer to CSLB Response 5A.

The impact of prohibited concomitant medications on the primary efficacy variable and on the per protocol (PP) population and sub-populations was determined as follows:

- *Narcotic Pain Medications:*
  Narcotic pain medications, as listed in Appendix IVa of SAP Version 2.0 for the final analysis, only resulted in imputation of a poor/failure outcome of the primary endpoint under the following conditions:
  - *If they were administered in the critical time period between start of randomized study medication and start of symptom relief, or 24 hours after start of randomized study medication*

    or
  - *If they were recorded on the CRF as prior to and ongoing after the start of study medication and there was no investigator comment (variable INVCMT) to confirm that the medication was not used during the critical time period.*

- *Androgens, Tranexamic Acid and Aminocaproic Acid:*
  The review of the closed database (based on the SAP Version 2.0 for the final analysis) confirmed that there were no changes in the dosing regimen of any of these medications during the critical time period between start of study medication and start of symptom relief in any subject. Therefore, according to protocol, none of these medications resulted in the imputation of a poor/failure outcome of the primary endpoint.
  Note: Androgens [variable SGANDROG] led to exclusion from the PP analysis if they were administered within 4 hours after the start of blinded study medication and if they had not been

used, or used at lower doses, before the study.

- *C1-INH and FFP (coded as "Plasma protein concentrate"):*
  *Two subjects (---**b(6)**----------) received FFP as concomitant medication prn, documented as "prior" and "ongoing" on the CRF. However, in both cases, the investigator response to a query confirmed that FFP was not administered during the critical time period between start of study medication and onset of relief (see file DCFs_site8_USA in CDROM subfolder Attachment 5B1+5B2). Therefore, the use of FFP did not lead to imputation of a poor/failure outcome.*
  All open-label C1-INH administrations documented in the concomitant medication CRF started more than 24 hours after start of study medication and therefore did not lead to imputation of poor/failure outcome of the primary endpoint (see CSLB Response 11).

- *Drugs Targeting the Biological Mechanisms of Action of C1-INH:*
  The review of the closed database (based on the SAP Version 2.0 for the final analysis) confirmed that no subject received "any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis."

Note: The definitions and calculations of the primary endpoint TtRel+ (variable TTRELP) are provided in the Reviewer Guide to the Database (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

Reviewer Comment

With regard to concomitant use of *Androgens, Tranexamic Acid and Aminocaproic Acid, the sponsor states "The review of the closed database (based on the SAP Version 2.0 for the final analysis) confirmed that there were no changes in the dosing regimen of any of these medications during the critical time period between start of study medication and start of symptom relief in any subject."* However, the sponsor has not provided in amendment 25 the method or field names by which they verified using the database(s) that the doses of these medications did not change between 5 hours prior to the time of administration of randomized blinded study medication and time to initial relief of symptoms. The sponsor was asked to provide this information during the teleconference held with the sponsor in May, 2009. Review of SDs submitted in subsequent amendments revealed that a single subject had the dose of androgen doubled prior to participation in the trial, so this was factored into imputing a 24 hour value for the primary endpoint in the FDA analysis of this subject.

Amendment 25 does not stand alone, in terms of containing a clear, complete, and detailed statement of how the sponsor performed the primary endpoint analysis. The brief outline found in the Reviewer Guide to the Database does not list all the field names of the variables that are required to perform the primary endpoint efficacy analysis. Subsequent amendments, submitted at FDA request, addressed this problem.

6. Please provide a single analysis database that contains all raw data and derived data fields needed to completely validate your primary efficacy endpoint of time to initial relief of symptoms.

Sponsor's Response

The derivation of the primary endpoint is a 2-step process. During Step 1, the onset of symptom relief (i.e., variables TOSREL and TTREL) is determined based on the subject's assessment of the HAE attack under study. During Step 2, the imputation of the primary endpoint TtRel+ is performed based on the use of blinded rescue study medication, open-label emergency study medication, and prohibited concomitant medications. In order to facilitate validation of this 2-step process and to avoid an overly complex dataset, CSLB considered it necessary to create two datasets (CRL_Q6A, CRL_Q6B) in response to CBER Comment 6. CSLB provides the dataset for Step 2 in the following three versions: CRL_Q6BO for the original analysis, CRL_Q6BR for the additional robustness analysis, and CRL_Q6c containing both datasets for comparison. These datasets are located in CDROM subfolder Attachment 6.

An algorithm for derivation of the primary endpoint TtRel+ based on the variables in datasets CRL_Q6A, CRL_Q6BO and CRL_Q6BR is provided in the Reviewer Guide to the Database (location: CDROM subfolder 3_Datasets and Programs\3.1_Reviewer Guide to Database).

From the latter document:

In order to compare the differences in the imputation of the primary endpoint variable TTRELP between the original analysis and the additional robustness analysis conducted to address CBER's Comment 5C of the Complete Review Letter, a new dataset CRL_Q6C was created. This dataset combines the classification of the concomitant medications according to Appendix IVa of the final SAP Version 2.0 of 26 October 2007 (variable CATEGORY) as well as the classification according to the extended list PROHMED.xpt for the additional robustness analysis (variable RCAT). For comparison, both primary endpoints TTRELP for the original analysis and RTTRELP for the additional robustness analysis are available in dataset CRL_Q6C.

Reviewer Comment

Amendment 25 does not stand alone, in terms of containing a clear, complete, and detailed statement of how the sponsor performed the primary endpoint analysis. The brief outline found in the Reviewer Guide to the Database does not list all the field names of the variables that are required to perform the primary endpoint efficacy analysis. Rather than provide FDA with a single database as requested, the sponsor states that 4 databases are needed to perform the primary endpoint analyses. They make reference to -b(4)- code for the primary analysis previously submitted, but do not provide the amendment number or location of this information. Neither the -b(4)- code nor a sufficiently detailed narrative has been provided to permit performance of the "robustness" analysis [main analysis] of the primary endpoint requested by FDA that includes all analgesics taken during the time window of interest in imputing poor/failure outcomes. Subsequent amendments addressed this deficiency.

7. Please indicate the date the blind was broken for phase II/III study CE1145_3001 (IMPACT I).

Sponsor's Response

The blind was broken on 2 November 2007 in compliance with the Standard Operating Procedures of the biometrics service provider, --b(4)--

Reviewer Comment

The date given by the sponsor for unblinding of the pivotal trial was just 7 days following the date of SAP version 2.0. The sponsor confirms elsewhere in the submission that SAP version 2.0 was never submitted to the IND.

8. Please indicate the date that the revised statistical analysis plan version 2.0 dated October 26, 2007 (approximately 1 month before the last subject completed the day 7-9 follow-up) was submitted to the IND.

Sponsor's Response

CSLB did not submit SAP Version 2.0 dated 26 October 2007 to the IND, but submitted it on 6 March 2008 in the original BLA submission (STN 125287/0, refer to CTD Module 5, Section 5.3.5.1.1-1.22, Appendix 16.1.9.20.2). Appendix IVa of this SAP contains the list of prohibited medication used for the final analysis.

The SAPs generated for Study CE1145_3001 are located in CDROM subfolder Attachment 8.

Reviewer Comment

Because the sponsor did not submit version 2.0 to the IND for FDA comment prior to unblinding the study, FDA has not accepted all changes in SAP version 2.0 compared to version 1.0, which had been filed to the IND. Note that version 1.0 did not contain a list of medications that would result in imputation of a "poor/failure" value of 24 hours for the primary endpoint, time to initial relief of HAE attack symptoms; however, the protocol discussed which classes of medications would result in imputation of a "poor/failure" value of 24 hours for the primary endpoint, as reflected in my original BLA review and in the CR letter.

9. Please provide a table and database that lists all subjects for whom, in the protocol-defined primary endpoint analysis, you have imputed a poor/failure value of 24 hours. Include for each subject in the table the specific reason for imputation of the poor/failure value of 24 hours (i.e., analgesic drug administered at 3.0 hours, which was prior to TTREL value of 3.5 hours; missing TTREL, etc.)

Sponsor's Response

The requested listings and datasets are located in CDROM subfolder *Attachment 9*. Separate listings and datasets have been generated based on:

- the original list of prohibited medications from Appendix IVa of the SAP Version 2.0 for the final analysis (*Listing Q9_24hour_poor_failure_endpoint_original* and dataset *CRL_Q9O*);
- the list *PROHMED.xpt* for the additional robustness analysis (*CBER Comment 5C*) that includes the additional medications suggested by CBER, e.g. non-narcotic pain medications (*Listing Q9_24hour_poor_failure_endpoint_robustness* and dataset *CRL_Q9R*).

Reviewer Comment

The original list of prohibited medications is considered useful only as a supportive analysis to the extent it can be verified that the dose of androgens, epsilon amino caproic acid, tranexamic acid, and products with a similar mechanism of action to any of the 4 known mechanisms of action of C1-Esterase Inhibitor were either not increased in dose (1st 3 drugs) or not taken during the time window of interest (last category). FDA emphasized the robustness analysis using the Prohmed.xpt medication list for its principal analysis of the primary endpoint, but noted that 2 medication with anti-emetic propoerties taken by subjects were not included by the sponsor in the Prohmed.xpt list. In addition, one subjects had the dose of androgen doubled prior to the study.

10. When you redo and resubmit your analyses of the primary endpoint, please use the actual times of administration of "any rescue medication" (including all "discouraged" and all 6 classes of "Non-permitted" medications) as indicated on hospital record source documents to impute values of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who received any such concomitant medications within the time frame from 5 hours prior to the time of administration of randomized CTM to "TOSREL" (time to initial relief of symptoms) and imputing a value of 24 or 4 hours, as appropriate, for any subjects with missing data for date/time of administration of such medications. This would be consistent with the feature of the protocol which specified to count as treatment failures subjects with missing data for time to initial relief of symptoms.

Sponsor's Response

Hospital records/source data to confirm the actual times of administration were collected from all subjects who, between 5 hours before and 24 hours after start of randomized study medication, received any of the concomitant medications included in the list PROHMED.xpt for the additional robustness analysis (location of PROHMED.xpt: CDROM subfolder Attachment 5B3b).

The results of the additional robustness analysis of the primary endpoint including these hospital records/source data are presented in CSLB Response 5C.

Note: According to the protocol, non-narcotic pain medications were not specified as exclusion criteria, because these medications are deemed ineffective for the treatment of acute HAE attacks

(see the Cover Letter including outside consultants' letters in CDROM subfolder 1_Cover Letter +Attachments A, B, C). Therefore, the concomitant use of these medications was not considered to have an impact on the assessment of the primary endpoint (time to onset of relief). For this reason, CSLB regards the requested re-analysis as an additional, exploratory robustness analysis that is not valid for the assessment of confounding factors influencing the time to onset of relief of an acute HAE attack treated with C1-INH.

Reviewer Comment

See my comment on sponsor's response to CR item 5A regarding non-narcotic analgesic use as concomitant medication. Amendment 25 lacks sufficient information to be able to readily verify robustness analysis referred to in sponsor's response to item 5C. This was addressed in subsequent amendments.

11. We note that 9 subjects are listed in the original submission ADCM concomitant medication database as having received "C1-INH" or "Berinert" and this is less than the total number of subjects in the study who received masked (blinded) rescue study medication, as listed in Table Q1c (24 in the placebo group, 13 in the Berinert 10 U/kg group, and 8 in the Berinert 20 U/kg group). Please clarify whether you imputed a "poor/failure" value of 24 (or 4, depending on the analysis) hours for all subjects who received any C1-Inhibitor product within 5 hours prior to the time of randomized CTM administration or prior to TOSREL (time of initial relief of symptoms), whether recorded as concomitant medication or as rescue study medication. When you resubmit the primary endpoint analyses requested above, please impute a "poor/failure" outcome of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who had any C1-Inhibitor listed on the CRF but for whom the start date and/or start time was missing.

Sponsor's Response

With respect to C1-INH administration, the concomitant medication dataset ADCM only includes subjects who received C1-INH as open-label concomitant medication (as documented on the corresponding CRF), and therefore specifically excludes the blinded rescue study medication that is instead tabulated and listed in BLA Module 5, Tables 11.97-100 and Appendix 16.2.5.2. The footnote to Table Q1c in Amendment 17 (submitted on 12 September 2008) indicates that the numbers of subjects mentioned in CBER Comment 11 (i.e., N=24, 13, 8) represent only the blinded rescue study medication.

In the final concomitant medication dataset ADCM submitted in Amendment 17, a total of 11 subjects received C1-INH as open-label concomitant medication (Subject --b(6)----------. Note: Dataset ADCM, as included in the original BLA submission, did not yet contain Subject -b(4)-, because the subject's observation period ended only after database lock for the BLA submission). The administration of C1-INH as open-label concomitant medication did not lead to imputation of a poor/failure outcome for the primary efficacy endpoint in any of these 11 subjects, for the following reason:

- *All 11 subjects had documented (CRF) start dates for the concomitant open-label C1-INH.*
- *Missing start times were imputed as 00:00 h of the respective dates for the purpose of time difference calculation.*

In fact, for all 11 subjects, the documented start dates for concomitant open-label C1-INH were

- *At least 2.5 days after administration of randomized study medication, and*
- *Always after time of start of relief (ToSRel; see the individual entries in Listing_Q15_All_C1INH_administrations in CDROM subfolder Attachment 15).*

Therefore, considering the long interval between start of randomized study medication and open-label concomitant C1-INH based on the documented start dates, the imputation of the missing start times as 00:00 h of the respective dates could not have had any impact.

In addition, there were no subjects who received C1-INH within 5 hours before start of randomized study medication (see Listing_Q15_All_C1INH_administrations referring to CSLB Response 15).

Consequently, there is no change between the original analysis and the additional robustness analysis for CBER Comment 5C with respect to the imputation of a "poor/failure" outcome for the primary endpoint due to the administration of open-label concomitant C1-INH.

Reviewer Comment

Noted.

12. It does not appear that you provided the requested analysis 1C of the breakdown by randomized treatment group of the use of "any rescue medication" as requested in our fax to you dated August 21, 2008, which did not restrict the time frame of administration of such potentially confounding concomitant medications. Please submit analyses in response to question 1C that include all:

    a) medications covered by "any rescue medication" anytime from 5 hours prior to ToS (time of start of study treatment) through day 7-9 of follow-up, and

    b) such medications administered from 5 hours prior to ToS through time to ***complete*** relief of symptoms.

Sponsor's Response

As medication given after symptom relief is not rescue medication by definition, CSLB believes that we provided the analyses as requested in CBER's 21 August 2008 fax. Therefore, CSLB conducted the following three analyses in response to CBER question 1C:

- *Frequency of blinded rescue study medication,*

- *Frequency of any rescue medication within 4 hours after start of blinded study medication (SGRESC), and*
- *Frequency of blinded rescue study medication before start of relief.*

Based on CBER's clarification in Comment 12 in the Complete Response Letter, CSLB is providing the requested analyses for verification of the original and the revised analysis of CBER question 1C of 21 August 2008 (Table_Q12 Medications_used_original and Table_Q12 Medications_used_robustness, Listing_Q12_ConcMed_list_original and Listing_Q12_ConcMed_list_robustness; all located in CDROM subfolder Attachment 12). These tables and listings include all medications defined as "any rescue medication" in Appendix IVa of SAP Version 2.0 for the final analysis (CDROM subfolder Attachment 8) and in list PROHMED.xpt for the additional robustness analysis (CDROM subfolder Attachment 5B3b) that were administered during the following time periods suggested in CBER's question 1C (21 August 2008 fax):

- *Between 5 hours before start of study medication and Day 7-9; and*
- *Between 5 hours before start of study medication and complete resolution of the attack under study.*

The abovementioned tables and listings were derived from datasets CRL_Q12O and CRL_Q12R that contain all concomitant medications, using the classification variable CLASS.

Reviewer Comment

Sponsor Table Q12 lists the number and percent of subjects by randomization group who received any of the PROHMED list of "any rescue medication" (defined by the sponsor as including discouraged medications (analgesics and anti-emetics) and "non-permitted" medications taken (a) anytime between 5 hours prior to ToS until day 7 to 9 (follow-up visit) and (b) anytime from 5 hours prior to ToS until and including ToSRel.

ITT population Statistic	Placebo	Berinert 10 U/kg	Berinert 20 U/kg	Total
number of subjects N (%)	42 (100)	39 (100)	43 (100)	
Rescue med until Day 7 to 9 yes N (%)	33 (78.6)	27 (69.2)	23 (53.5)	
Rescue med until ToRes yes N (%)	28 (66.7)	24 (61.5)	18 (41.9)	
Rescue med until 4h yes N (%)	10 (23.8)	6 (15.4)	11 (25.6)	

Note that FDA's review of SDs revealed inaccuracies in this table.
It can be seen, however, using the sponsor's analysis, that the number of subjects who took discouraged or non-permitted medications until 4 hours following ToS was

comparable in placebo and 20 U/kg randomization groups, but that 10 more subjects (an additional ~ 25%) in the placebo group took such potentially confounding medications in the placebo group than in the higher dose group prior to ToRes and also prior to day 7 to 9 f/u. This analysis lends support to the conclusion that the product is more effective than placebo at the higher dose.

13. In amendment 16 submitted September 3, 2008 in response to our August 21, 2008 information request item 1C, you cited Table 10.5 in support of the first bullet in your reply to our request for the analysis of "The proportion of subjects in each randomization treatment group that received open label CTM or rescue medication or analgesics or anti-emetics in each randomization group."

    This table shows a total of only 4 subjects across the 3 randomization groups who received analgesics/anti-emetics/C1-Inhibitor as concomitant medications.

    This total conflicts with the revised information on the use of concomitant medications presented in the safety update.

    Please provide a printed table and an analysis database with the subject ID numbers, TTREL, TTRELP, time to complete relief of symptoms, the difference between the time randomized CTM is administered and the start date and time of open label CTM or blinded rescue medication or analgesics or anti-emetics were given (irrespective of whether they were begun before or after initial relief of symptoms). **Consistent with the protocol-defined primary endpoint analysis, please include all drugs/therapeutic agents that have analgesic or anti-emetic pharmacologic properties, regardless of whether you have previously classified them as analgesics or anti-emetics.** This should include, but not necessarily be limited to the following concomitant medications in addition to open label or masked CTM, as taken from your safety update, medications you have classified as:

    - analgesics (4/42 placebo subjects, 4/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects),
    - fentanyl (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
    - ibuprofen or ketorolac tromethamine (1/42 placebo subjects, 2/39 Berinert 10 U/kg subjects, and 1/43 (%) of Berinert 20 U/kg subjects),
    - vicoprofen (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
    - ASA (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 0/43 of Berinert 20 U/kg subjects),
    - prednisone (0/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects),
    - promethazine (2/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 2/43 (4.7%) of Berinert 20 U/kg subjects),
    - hydroxyzine (1/42 placebo subjects, 0/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects),

- plasma protein fraction (0/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects), and
- medications you have classified as antiemetics/antinauseants (1/42 placebo subjects, 1/39 Berinert 10 U/kg subjects, and 1/43 (2.3%) of Berinert 20 U/kg subjects).

Sponsor's Response

As stated in *CSLB Response 12*, there was a misunderstanding between CSLB and CBER regarding CBER's 21 August 2008 request. Therefore, Table 10.5 did not provide the information CBER was expecting: The total of 4 subjects across the 3 randomization groups in Table 10.5 is only a subset of the overall study population and only includes subjects who received prohibited concomitant medications (analgesics/anti-emetics/open-label C1-INH/FFP) between the start of study medication and 4 hours thereafter and is also only based on the prohibited medications listed in Appendix IVa of final analysis SAP Version 2.0 (i.e., variable SGANA).

The analysis required to resolve the conflict pointed out in *CBER Comment 13A* is located in CDROM subfolder *Attachment 12* (see also *CSLB Response 12*).

CSLB Response 13B:

CSLB is providing a listing and dataset (Listing_Q13_Concomitant_medication_list_robustness, dataset CRL_Q13R) with the requested data (use of concomitant medications per subject) that is based on the list PROHMED.xpt. These supporting files are located in CDROM subfolder Attachment 13B. The corresponding listing and dataset for the original analysis, i.e., Listing_Q13_Concomitant_medication_list_original and dataset CRL_Q13O, are also located in CDROM subfolder Attachment 13B.

Reviewer Comment

Noted. See my comment on Sponsor's response to CR item 12.

Unfortunately, the sponsor did not understand the intent of the requested table. The sponsor provided in the Listing Q13 the start time of the potentially confounding medications even when it was several years before the study began. Rather, what was desired was the "start" time after the current attack had begun, in order to verify whether the medication was taken in the time window of interest (from 5 hours prior to ToS to either time of complete relief of symptoms or day 7-9 of f/u).

14. From table 11.2.1 it is apparent that 3 placebo subjects received "study rescue medication, and analgesics/anti-emetics/open label C1-INH/FFP" between 1 and < 4 hours from when masked randomized study CTM was administered. The table shows an additional subject who received prohibited medication at time zero. Field TTRESC in database ADCM shows only subject --b(6)-- received rescue medication during the time window 0 to < 4 hours (1.67 hours). No value is given for this subject in field TTANA ("Time to [sic] between start of randomized CTM to start of analgesics/anti-emetics/C1-INH/FFP concomitant medication in hours." From inspection of the field values for TTANA, subject

--b(6)-received the anti-emetic prothiazine at 1.5 hours and subject -b(6)-- received the anti-emetic Phenergan at 3.07 hours.

Please redo table 11.2.1 after assigning "poor/failure" outcome values of 24 (or 4 hours, as appropriate, depending on the analysis) to subjects with missing data for the start date/time of administration of "any rescue medication" and using updated times of administration of "any rescue medication" given between 5 hours prior to ToS until ToSRel as obtained from hospital medication source records.

Sponsor's Response

Notes to *CBER Comment 14*:
(1) According to the clarifying email from N. Cagungun (CBER) of 02 February 2009, "Table 11.2.1" actually means "Figure 11.2.1".
(2) Subject "-b(6)-" is Subject --b(6)-- at Center b(4), as there is no Center b(4) with Subject -b(6)-.

Missing TTANA value for Subject -b(6)-:
For this subject, the TTANA value is missing because the subject received no concomitant medication fulfilling the criteria for calculating TTANA. The blinded rescue study medication the subject did receive is not taken into account as a concomitant medication for calculating TTANA, but for calculation of the separate variable TTRESC (i.e., time between start of study medication and blinded rescue study medication; see *CSLB Response Appendix 6B* and *CSLB Response Appendix 7*).

Subject who received prohibited medication at time zero (Subject -b(6)-):
This additional subject in Figure 11.2.1 is Subject -b(6)- (Berinert 10 U/kg) who was censored at 0 hours, because the start time of Phenergan (promethazine hydrochloride) was unknown and set to the earliest possible value of 0 hours for this sensitivity analysis. This sensitivity analysis performed in Figure 11.2.1* was intended to analyze the time to onset of symptom relief using survival analysis methods. TtRel was censored at the time of any rescue medication (i.e., blinded rescue study medication or analgesics/anti-emetics or other prohibited medication).

Note: "Censored at time X" means that onset of relief took at least up to time X, but the exact time of onset of relief is not known. In the case of Subject -b(6)-, this means that it is unknown (and it cannot be known) how long the time to relief would have been without the concomitant medication; therefore, censoring the subject at 0 hours means that this subject does not contribute any information to the sensitivity analysis, and it does not mean that the subject is included in the analysis with the best possible value of 0 hours. For the primary analysis, the time to onset of relief TtRel+ for this subject was set to the poor/failure outcome of 24 hours (Figure 11.1.1).
* Table 11.17.3 and Statistical Appendix 16.1.9.4.1 only refers to the comparison of Berinert 20 U/kg and Placebo.

Sensitivity analysis, Figure 11.2.1:
It was the specific purpose of the sensitivity analysis in Figure 11.2.1 to assess if there is any large difference to the primary analysis if times to onset of relief are censored at the time of rescue medication administration. The interpretation of the impact of rescue medication on time to onset of relief in this sensitivity analysis is as follows: It cannot be known at which time relief would

have started if the subject had received no rescue medication, rather than interpreting the administration of rescue medication as treatment failure as done in the primary analysis.

CSLB revised the sensitivity analysis as requested by CBER (see the updated Figure 11.2.1 in CDROM subfolder *Attachment 14*: *Table_11.17.3_new_robustness*, *Figure 11.2.1_new_robustness*; dataset *CRL_Q14R*). However, it should be noted that the requested procedure of setting all censored values to a poor/failure outcome would result in a similar analysis as already presented in the BLA for the primary endpoint. Therefore, CSLB does not consider it sensible from a statistical point of view to set single values to 24 hours in the requested analysis while censoring the other values.

Also, CSLB is providing corrected versions of Figure 11.2.1, Table 11.17.3 and Statistical Appendix 16.1.9.4.1-3 (*Figure 11.2.1_new_original, Table 11.17.3_new_original,* and dataset *CRL_Q14O* in CDROM subfolder *Attachment 14*) for the following reason: One subject (Subject -b(6)-, Berinert 20 U/kg group) received open-label emergency study medication at 2:09 hours after start of randomized, blinded study medication; this subject's outcome for the primary endpoint TtRel+ was set to 24 hours; however, by mistake it was not censored in Figure 11.2.1, but was included with the non-censored TtRel value of 4.65 hours (also see *CSLB Response Appendix 12*).

Reviewer Comment

Noted. Because the analyses using censoring lose all contribution from the subject who was censored at time zero, analyses without censoring but which impute poor/failure values of 24 hours for the primary endpoint and for subjects with missing primary endpoint data are considered by FDA to be more informative. From the information provided, it seems there were 4 subjects who would have received poor/failure imputed outcomes of 24 hours, due to having received "study rescue medication, and analgesics/anti-emetics/open label C1-INH/FFP" between 1 and < 4 hours from when masked randomized study CTM was administered (ToS) ,using the sponsor's SAP version 2.0 analysis method

15. We note that in the concomitant medication original database ADCM, there were a total of 9 subjects listed who received either "C1-INH" or "Berinert" as concomitant medications (subject nos. ------b(6)----------). The study report discusses a single subject who received open-label Berinert during the initial 4-hour period. Please provide a printed table and database listing all subjects who received C1-Inhibitor/Berinert at any time during the trial together with the difference in time between the time zero administration of masked randomized CTM and the administration of C1-Inhibitor/Berinert, TTREL, TTRELP, and time to complete resolution of symptoms. Please discuss the impact, if any, of the administration of C1-Inhibitor/Berinert as a concomitant medication on each study endpoint, including time to complete relief of symptoms.

Sponsor's Response

CSLB Response 15:

CSLB Response 11 explains the timing of administration of concomitant open-label C1-INH (in dataset ADCM) and why it has no impact on the primary endpoint.

The subject discussed in the clinical study report is Subject -b(6)- (Berinert 20 U/kg group) who received open-label C1-INH as emergency study medication (according to the protocol in case of a laryngeal attack) during the 4-hour time window after administration of randomized study medication. For this subject, the primary efficacy variable was therefore set to the poor/failure outcome of 24 hours (see *CSLB Response 14*).

The data from the two other subjects who received C1-INH as open-label emergency study medication were not further discussed in the clinical study report due to the following:

- Subject -b(6)- (randomized to the 10 U/kg group) received only the open-label emergency study medication, but received no randomized, blinded study medication. This subject was excluded from the intention-to-treat (ITT) population and thus excluded from the efficacy analyses.
- Subject -b(6)- (Berinert 20 U/kg group) received the open-label emergency study medication more than 13 days after randomized study medication and also after start of relief. Therefore, these data did not have an impact on the efficacy analyses.

As requested, *Listing_Q15_All_C1INH_administrations* and dataset *CRL_Q15O* (location: CDROM subfolder *Attachment 15*) contains all C1-INH administrations including time points, TtRel and TtRes for all subjects receiving C1-INH at any time. This includes C1-INH administered as:

- the randomized, blinded study medication,
- the blinded rescue study medication,
- the open-label emergency study medication, and/or
- open-label concomitant medication (all administered after start of relief, and after complete resolution [exception: Subject -b(6)-*]).
  *The open-label concomitant C1-INH in Subject -b(6)-was administered about 7 days after the administration of blinded study medication and time of start of relief; however, no time of complete resolution of symptoms is documented for this subject.

Reviewer Comment

Noted.

16. You state on page 90 in section 12.3.2 in the interim study report for open-label extension study CE1145_3003 (IMPACT II) "As there were no deaths, no related SAEs, and no other significant AEs, detailed narratives are available upon request since this information does not affect the safety claims made in this report." Your study report does not identify the subject number of the individual who experienced this treatment-emergent reaction which was attributed to administration of Berinert or provide any details as to the nature of the "infusion related reaction." Please provide a detailed narrative of the "infusion related

reaction" that led to premature discontinuation of administration of Berinert and premature discontinuation from the study.

Sponsor's Response

CSLB Response 16:

The subject is Subject -b(6)-. As requested, a detailed narrative is provided below.

Narrative:

At the time of treatment for an acute HAE attack (12 April 2006), Subject -b(6) (48-year-old female) experienced a non-serious treatment-emergent AE of infusion-related reaction.

Medical history includes HAE, menopause, depression related to menopause, recurrent urinary tract infection, and rosacea.

Concomitant medications / start dates include:

- Doxycycline 50 mg QD / 3 April 2006 (for rosacea treatment)
- Zoloft (Sertraline hydrochloride) 50 mg QD / no start date reported
- Tylenol (acetaminophen) *prn* / no start date reported

The subject received open-label C1-INH under Protocol CE1145_3003 on 12 April 2006 at 11:47 (Note: Times are provided in the 24-hour format) via slow push at 4 mL/minute. After only 3.6 mL of study medication infusion, the infusion was abruptly halted at 11:49 due to the subject's report of "not feeling well." At the onset of the AE, the subject reported a headache and severe pain rating 10/10. The investigator instructed the study coordinator to monitor the subject and complete the remaining infusion if the subject desired.

The following table reports the subject's blood pressure (BP), heart rate (HR), and blood oxygen saturation (O_2 SAT) at the time of the AE:

Time	BP	HR	O_2 SAT
11:52	160/100	84	-
11:57	150/90	88	99%
12:02	130/90	67	99%
12:15	130/88	66	99%
12:34	120/92	-	-

After approximately 30 minutes, the subject did feel better, but did not wish to continue the study medication infusion. Blood samples were drawn at 12:34 when the subject reported that all HAE symptoms had resolved. The subject reported via phone to the clinic at 16:25 that, although she felt completely recovered from the AE, the HAE symptoms had returned to baseline severity at the subject's arrival at the clinic. The subject did not wish to seek treatment for the HAE at that time.

During 3 subsequent phone contacts on 13 April 2006, the subject informed the site of persistent HAE symptoms with similar baseline severity. The subject refused treatment.

Unlike previous infusions, the study medication infusion on 12 April 2006 was administered into the subject's hand. The subject reported "feeling the drug this time."

The subject stated experiencing similar symptoms in the past when receiving IV contrast dye. The subject also recently began taking Doxycycline (50 mg QD).

Assessment of the Investigator:

Prior to laboratory results taken during the AE, the investigator recorded that the AE (non-serious) had a possible relation to study medication. Laboratory results showed elevated serum tryptase that did not reflect systemic mastocytosis based on negative bone marrow biopsy results and c-kit gene mutation test. The diagnosis was mild erythrocytosis. No cause could be found for the subject's elevated serum tryptase.

Reviewer Comment

This subject reported a headache and severe pain rating 10/10, starting during a < 5 minute infusion of study product, which was prematurely halted and not restarted due to the AE. Her BP was elevated to 160/100 five minutes after the start of the infusion, and normalized within 23 minutes of observation. The subject likened the AE to how she had felt during prior infusion of IV radiographic contrast, but it is not stated whether she was considered to have a history of reaction to IV radiographic contrast or not. She had been taking doxyclycline for 9 days at the time of the AE, as well as Zoloft and Tylenol (start dates unknown). Serum tryptase was elevated, a bone marrow aspiration was negative for systemic mastocytosis, and the subject had mild erythrocytosis. The classification of the AE as an acute infusion reaction appears to be accurate. While an acute hypersensitivity reaction may be considered, a hypertensive reaction of unknown etiology may have accounted for the headache and severe pain. Although the headache may have been related to the hypertension, the degree of BP elevation was only mild to moderate.

17. Subject -b(6)- experienced a severe AE recorded as an exacerbation of hereditary angioedema. This subject received rescue medication on March 20, 2006 at "61500," according to column "RESCSTTI" in the ADAEFDA database. Please explain what is meant by "61500".

Sponsor's Response

CSLB Response 17:

The variable RESCSTTI is formatted in a b(4) time format in all datasets CSLB has submitted. The unformatted value of 61500 converts to a formatted value of 17:05 h (5:05 p.m.), with the following calculation: 61500 seconds after 0:00:00 h = 1025 minutes = 17,0833 hours = 17 hours, 5 minutes = 17:05 h).

Reviewer Comment

Noted.

18. Please provide additional immunogenicity data from a total of at least 40 HAE subjects who have received multiple exposures of the product. Antibodies against C1-Inhibitor should be measured at baseline and after 3, 6, and 9 exposures to the product, or every 3 months, whichever comes first, over a period of up to 12 months. Subjects with antibodies positive by -b(4)- should be tested for inhibitory antibodies using a validated assay. When submitting the data please describe in detail attempts to correlate treatment-emergent antibodies with AEs.

Sponsor's Response

CSLB Response 18:

The required immunogenicity data would come from subjects who are enrolled in the extension study CE1145_3003 (I.M.P.A.C.T. 2) that CSLB is presently conducting.

As agreed upon with CBER, CSLB is to submit antibody data from samples available as of 5 March 2009.

At the time when the amendment for collection of additional immunogenicity data was approved for Study CE1145_3003, 57 subjects were enrolled. In the meantime, 24 subjects have dropped out of the study for various reasons (e.g., enrolled into another study, lost to follow-up). Of the remaining 33 subjects, 31 are willing to donate blood for the requested immunogenicity testing. Therefore, CSLB would be able to provide data from a maximum of 31 subjects.

A total of 923 HAE attacks have been treated in Study CE1145_3003, with a mean number of 16 attacks per subject. As of 23 March 2009, CSLB has analyzed 27 samples from 26 subjects (range of attacks per subject: 1 to 145 attacks) available for antibody screening after multiple treatments.

Six of the 26 subjects were tested above cut-off to anti-C1 antibodies, thereof 5 subjects already at baseline of Study CE1145_3003. Four of the 5 subjects who tested above cut-off to anti-C1 antibodies at baseline of Study CE1145_3003 already tested above cut-off at screening for Study CE1145_3001, i.e. before receiving the first dose of study medication.

Subject -b(6)- switched from below cut-off at baseline to above cut-off for IgM in the isotyping testing after treatment for 12 attacks during Study CE1145_3003. The last time the subject was treated was 19 April 2008. The antibody test was conducted on 23 February 2009. As of today, no information on concomitant AEs is available yet. However, a relationship to Berinert administered 10 months earlier is unlikely, because an early emerging antibody such as IgM is expected to be detected for only a short duration after study drug administration.

Reviewer Comment

Two subjects out of 26 evaluated from the extension study CE1145_3003, **as of 23 March 2009, had treatment-emergent anti-C1-Esterase-Inhibitor antibodies. One subject became antibody positive during the extension after treatment with test product for 12 attacks, but the subject was IgM positive 10 months after the last exposure, which is unexpected. It appears the other subject became antibody positive between screening for the pivotal study and testing during the extension study. Although the mean number of attacks treated with product per subject in the extension study is 16, the range goes down to 1. Thus, from the sponsor's summary response the number of subjects tested for antibodies who had had multiple exposures to the investigational product cannot be discerned.**

It is encouraging that no neutralizing antibodies have been detected in subjects receiving the test product thus far.

19. Please submit data from at least 40 subjects for routine chemistry, including renal and liver function and aminotransferases, hematology, and urinalysis, including microscopic examination of urine sediment, from following single and multiple dose exposure to the product and compare these to baseline values.

Sponsor's Response

CSLB Response 19:

CSLB requests that the information from available subjects can be submitted as a post-approval commitment in the final clinical study report for extension study CE1145_3003 (I.M.P.A.C.T. 2) that is currently scheduled for December 2010.

Reviewer Comment

I recommend the sponsor submit interim data at this time in response to this CR letter item. It is reasonable to expect that some routine safety laboratory data following exposure to the product should be included in an original BLA. [Interim safety data was submitted on FDA re-request in a subsequent amendment and did not suggest new safety signals.]

LABELING

20. We reserve comment on the proposed labeling until the application is otherwise acceptable.

Sponsor's Response

CSLB Response 20:

CSLB will respond to additional comments concerning labelling as they are received.

Reviewer Comment:

The sponsor is asked to provide a revised draft package insert at this time, based on CBER's comments conveyed to the sponsor by fax on 05 November 2008.

APPENDIX TO FDA CR LETTER

- Inspection of original submission database ADCM reveals that the majority of subjects who received concomitant medications with analgesic or anti-emetic pharmacologic properties have missing values for their starting date and time. Thus, it is not possible to determine for these subjects whether these subjects should be classified as poor/failure outcomes and whether to impute 24 values for TTRELP (TTREL+) for these subjects.

Sponsor's Response

CSLB Response Appendix 1:

Please refer to *CSLB Response 5A* for explanations of the missing values for start date and time.

Reviewer Comment

See my comments on sponsor's response to CR item 5.

- In the original submission efficacy database, the field heading "SGANA" is defined "SG [subgroup] with/without analgesics/anti-emet/C1." We note that among the 65 or more subjects who received "any rescue medication" by our count in the original submission concomitant medication database ADCM, that only 4 subjects (Nos. --------b(6)----------) are listed has "with" "analgesics/anti-emet/C1" for this variable. Please explain this discrepancy.

Sponsor's Response

CSLB Response Appendix 2:

As explained in *CSLB Response 13A*, the subgroup SGANA (variable SGANA = yes) included subjects with analgesics/anti-emetics/open-label C1-INH/FFP administration

- Starting between the start of study medication and 4 hours thereafter

  and

- Comprising only those analgesics/anti-emetics listed in Appendix IVa of the SAP for the final analysis, Version 2.0 (location: CDROM subfolder *Attachment 8*), i.e. comprising *narcotic* analgesics.

Reviewer Comment

SGANA turns out not to be very useful because the time window for evaluating the "analgesics/anti-emetics/open-label C1-INH/FFP" does not begin 5 hours before ToS and because the use of non-narcotic analgesics are not taken into account.

- In the original submission efficacy database, the field heading "SGRECS" is defined "SG [subgroup] with/without any rescue medication." We note that among the 65 subjects who received "any rescue medication" by our count in the original submission concomitant medication database ADCM, that 37 subjects were incorrectly classified as not having received "any rescue medication." Among the "discouraged" or "non-prohibited" medications these subjects received were morphine, Demerol, phenergan, and odanosetron, among others. Please comment.

Sponsor's Response

CSLB Response Appendix 3:

The SAP specifies that the subgroup variable SGRESC is only to be derived for subjects regarding the administration of medications between the start of study medication and 4 hours after start of study medication, as follows:

> "Subjects with / without rescue medication (SGRESC)
> The subgroup "with" rescue medication will comprise subjects with rescue medication administration after at least 4 hours according to the protocol as well as subjects receiving medication not permitted under the protocol regarding analgesics/anti-emetics or open-label C1 INH concentrate during the first 4 hours."

The SAP for the 1st interim analysis (Version 2.0 **[Reviewer Comment: The sponsor likely means Version 1.0]** of 01 December 2006) and the SAP for the final analysis (Version 2.0 of 26 October 2007) specify in addition that "any rescue medication" includes the blinded rescue study medication as well as analgesics, anti-emetics, C1-INH and/or FFP.

Therefore, the meaning of the term *all / any* rescue medication in the definition of SGRESC is different from the following subgroup definitions:

- the subgroups defined by the use of blinded rescue study medication only (e.g., the After-4 hour Safety Populations);
- The subgroups defined by the use of other rescue medications only (i.e., subgroup SGANA of subjects receiving analgesics, anti-emetics, open-label C1-INH and/or FFP).

The term *all / any* rescue medication for SGRESC does not include all medications on the prohibited medication list administered at any *time*, but any *kind* of rescue medication *administered during the 4-hour period after start of randomized study medication*. In addition, the SGRESC subgroup definition refers to the original "non-permitted" medication list in Appendix IVa of the SAP for the final analysis, Version 2.0.

Thus, subjects receiving analgesics (even those listed in Appendix IVa of the SAP Version 2.0) might not appear in the SGRESC subgroup because they did not receive these medications within the 4-hour period after start of randomized study medication.

The restriction to the 4-hour period for SGRESC was applied, because it may be questionable *at least* for the primary efficacy variable whether the use of drugs after the time of start of relief is useful to define this subgroup. Subgroup definitions are usually based on a prognostic factor, i.e., the subgroup level for an individual subject should be known already at the start of study medication. Otherwise, the comparison of groups within subgroups may be biased, because the subgroup level could be a consequence of the outcome, rather than a possible reason for the outcome (i.e., a prognostic factor).

The updated DEFINE.pdf documents clarify that the variable SGRESC was restricted to the 4-hour period (see DEFINE_FUCRL.pdf in CDROM subfolder *3_Datasets and Programs\3.3_Original analysis [revised database]\Datasets* and DEFINE_FUCRL_ROBUST.pdf in CDROM subfolder *3_Datasets and Programs\3.4_Robustness analysis [revised database]\Datasets*).

Reviewer Comment

SGRESC turns out not to be very useful because the time window for evaluating the "analgesics/anti-emetics/open-label C1-INH/FFP" does not begin 5 hours before ToS, because it ends 4 hours after ToS in regard to consideration of potentially confounding concomitant medications, and because the use of non-narcotic analgesics are not taken into account.

- In partial response (September 3, 2008) to question 1A of our information request fax dated August 21, 2008, you state "The related Kaplan-Meier curve will be identical to Figure 11.1.1 of the clinical study report for the primary analysis variable if restricted to the 4 hour period …" Thus, it appears that the analysis method you described in Amendment 17 was the same method used for the primary endpoint analysis that was to have been done according to the protocol, except that our August fax asked you to impute a value of 4 hours rather than 24 hours for "Subjects receiving open label clinical trial material (CTM) or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms." According to the "DEFINE.PDF" document submitted as part of Amendment 17, derived variable, "CMPPFL" is defined to a value of "'Y' if concomitant medication is allowed by protocol in the given time window." Please clarify the time window used to determine values for CMPPFL.

Sponsor's Response

CSLB Response Appendix 4:

For the derived variable CMPPFL, the time window of 4 hours after the start of randomized study medication was used. In the concomitant medication dataset ADCM, CMPPFL was derived for *each* concomitant medication as follows, according to Appendix IVb of the SAP for the final analysis, Version 2.0:

- CMPPFL was set to "N" (no) if a subject received open-label C1-INH or FFP within the 4-hour time period after start of randomized, blinded study medication. In this case, the subject was excluded from the PP Population.
- CMPPFL was set to "N" (no) if a subject received androgens, or tranexamic acid, or

aminocaproic acid within the 4-hour time period after start of randomized, blinded study medication at a dose higher than that taken before start of study medication, as documented on the "prior/concomitant medication" CRF. In this case, the subject was excluded from the PP Population.

- In all other cases, CMPPFL was set to "Y" (yes), i.e., concomitant medication is allowed by the protocol within the 4-hour time window.

CMPPFL was included in all other datasets on a subject level, i.e., CMPPFL was set to "N" for a subject if any concomitant medication in this subject was flagged as CMPPFL="N" (no). In this case, this subject was excluded from the PP population.

A description of the derivation of variable CMPPFL is also available in DEFINE_FUCRL.pdf (location: CDROM subfolder *3_ Datasets and Programs\3.3_Original analysis [revised database]\Datasets*) and DEFINE_FUCRL_ROBUST.pdf (location: CDROM subfolder *3_Datasets and Programs\3.4_Robustness analysis [revised database]\Datasets*).

For the calculation of the primary endpoint with respect to concomitant medication, CMPPFL was not used, but only the variables TOANALG and CMANALG (CMANALG is set to "Y" if an analgesic/anti-emetic is given during the first 24 hours, i.e., if TOANALG was calculated, CMANALG is set to "Y").

Reviewer Comment

In the original submission and 1st review cycle amendments, it was not at all clear that variable CMPPFL was not used for the sponsor's primary endpoint analysis. CMPPFL is yet another derived variable that seems not to be very useful.

- Although the cover letter to Amendment 17 dated 12 September 2008 states "The purpose of this submission is to supply a complete response to item 1, it is unclear from inspection of Attachment 3, "Table of Contents for PDF documents," whether such a response was provided, either in the form of a narrative discussion or tables or figures responding to FDA item 1A request.

  The requested item 1A analysis from Amendment 17 read as follows:

  > Kaplan-Meier Curves for the high dose and placebo groups of the primary endpoint through 4 hours with corresponding p value for the difference in Kaplan-Meier curves. The exclusion of data beyond 4 hours avoids the artificial inflation of p values that occurs when a value of 24 hours is assigned to subjects who received rescue medication or open label CTM or analgesics or anti-emetics after 4 hours and prior to initial relief of attack symptoms. Mean and median times to initial relief of symptoms that include imputed 24 hour values and their associated p values should be deleted. Subjects receiving open label CTM or rescue medication or analgesics or anti-emetics before 4 hours and prior to initial relief of symptoms would be assigned an imputed time to initial relief of 4 hours [emphasis added.]

Table Q1a1.2 is described in your "Table of Contents for PDF documents" of Amendment 17 as "Time to start of relief: Time to start of relief (TrRel+a1) with censoring of subjects at 4 hours who received rescue study medication or open label CTM or analgesics or anti-emetics (before or after 4 hours) Generalized Wilcoxon test and Log-rank test between placebo and Berinert P, Dosage group II (2- U/kg b.w.)." This seems to conflict with with the information at the top of Kaplan-Meier plot Figure Q1a.1, which states it is based on the same derived data field, TtRel+a1. The title of this figure reads "Figure Q1a.1: Kaplan Meier Graph: Time to start of relief (TtRel+a1) with censoring of subjects at 4 hours who received rescue study medication or open label CTM or analgesics or anti-emetics (before or afer 4 hours **but before start of relief**) – ITT population [emphasis added]." Please clarify.

Sponsor's Response

CSLB Response Appendix 5:

Amendment 17 (submitted on 12 September 2008) refers to Attachment 16 in Amendment 16 (submitted on 03 September 2008) where only a partial response to question Q1a was provided. The "Table of Contents for PDF documents" did not include the figures. However, the tables and figures were indeed sent with Amendment 17. *CSLB Response Appendix 8* explains that information was inadvertently missing from the CDROM in Amendment 17.

Both Table Q1a.1.2 (as well as Table Q1a.1.1) and Figure Q1a.1 refer to the same variable (TtRel+a1 or TtRelPa1, which have identical values), i.e., the "time to start of relief with censoring of subjects at 4 hours who received rescue study medication or open-label CTM or analgesics or anti-emetics (before or after 4 hours but before start of relief)". For consistency, the title of Table Q1a.1.2 (as well as of Table Q1a.1.1) has been updated. The same applies to Table Q1a.2.1 and Table Q1a.2.2 to be consistent with Figure Q1a.2 and the respective Statistical Appendices provided in Amendment 17.

Updated tables with the corrected titles are located in CDROM subfolder *Attachment Appendix 5*.

Note: All subjects whose TtRel was >4 hours received rescue study medication before time of start of relief. Therefore, there is no difference between the number of subjects censored at 4 hours and the number of subjects set to 24 hours in the original primary analysis.

Reviewer Comment

Noted. The sponsor clarified that the definition of the key variable Table Q1a1.2 as described in its "Table of Contents for PDF documents" of Amendment 17 should have read "time to start of relief with censoring of subjects at 4 hours who received rescue study medication or open-label CTM or analgesics or anti-emetics (before or after 4 hours <u>but before start of relief</u>)."

- In addition, item 1 of our August 21, 2008 fax stated "Please describe which specific data fields in which databases may be used to generate the above analyses. If derived data fields have not been provided to permit the direct calculation of the above analyses, please provide

them together with a list of expanded data field definitions and the b(4) code for calculating the derived data fields." Your response appears to be incomplete, in that:

- We note that in Amendment 17 you do not appear to have provided a database to permit verification of your response to requested analysis 1C from our August 21, 2008 information request fax. [A]

- In Amendments 16, dated September 3, 2008, and in Amendment 17 dated September 12, 2008, it is not clear whether you have provided the derived data field for the difference between the time of blinded CTM administration (ToS) and the start time of administration of prohibited analgesics, anti-emetics, open-label C1-Inhibitor, and masked rescue study medication (see FDA request No. 4 in our 21 August 2008 fax). In your answer to item 4 you discuss TTANA, which is defined as "Time to [sic] between start of randomized CTM to start of analgesics/anti-emetics/C1-INH/FFP concomitant medication in hours." From this definition it is not clear whether masked CTM (including masked rescue placebo for the 20 U/kg Berinert randomization group) is included in this variable and IN TOANALG in Concomitant Medication database ADCM. Please clarify. [B]

- A derived data field that would include open label C1-INH and rescue study CTM ("all study rescue medication") as well as analgesics, anti-emetics, and any of the 6 classes of medications "Non-permitted" by the protocol (page 21, section 5.4) and supporting raw data fields showing the time and date of administration of these medications would help us to determine whether you have correctly imputed 24 hour (or 4 hour, as appropriate, depending on the analysis) poor/failure values for the primary endpoint, time to start of relief of HAE attack symptoms for the appropriate set of subjects. This is because only if this time difference equals or is less than TTREL should a poor/failure value of 24 hours be imputed for the primary endpoint, according to the study protocol. [C]

Sponsor's Response

CSLB Response Appendix 6A:

As explained in *CSLB Response 12*, CSLB believes that we provided the analyses as requested in CBER's 21 August 2008 fax and therefore provided no additional dataset in Amendment 17 for question 1C. However, based on CBER's clarification in *Comment 12* of the 5 December 2008 Complete Response Letter, the dataset for verification of the original and the revised analysis for question 1C is now provided in CDROM subfolder *Attachment 12*.

CSLB Response Appendix 6B:

Throughout the study documentation, the term "rescue study medication" denotes the blinded rescue study medication only (Berinert or Placebo), i.e., this does not include "analgesics/anti-emetics/open-label C1-INH/FFP" used and documented as concomitant medications. Therefore, the blinded rescue study medication was not included in the derivation of the variables TOANALG or TTANA. In addition, as explained in *CSLB Response 11*, the concomitant medication "open-

label C1-INH" does not include the protocol-specified emergency study medication (open-label Berinert) that could be given in case a laryngeal attack started during the abdominal/facial attack under study (e.g. Subject -b(6)-; see *CSLB Response 15*).

In contrast, the variables for the date/time of blinded rescue study medication are RESCSTDI and RESCSTTI, and **the variable for the calculated time *to* rescue study medication (i.e., time between start of blinded study medication and blinded rescue study medication) is TTRESC**.

The variables for the date and time of emergency study medication are EMSTDI and EMSTTI, respectively. **The calculated time *to* emergency study medication (i.e., time between start of blinded study medication and emergency study medication) was not derived as a permanent variable.**

In the new dataset generated for *CBER Comment 6* (CRL_Q6BR), **the variable CATEGORY includes information on the 3 types of study medication (i.e., blinded study medication, *blinded rescue* study medication, and *open-label emergency* study medication) as well as on any concomitant medications.** In addition, dataset CRL_Q6BR includes start date/time (variables EFXSTDI and EFXSTTI) as well as **the calculated time between start of blinded study medication and the respective event (variables DIFF and DIFFH)**.

The updated variable definitions for the revised database are provided in **DEFINE_FUCRL.pdf** for the original analysis (location: CDROM subfolder *3_Datasets and Programs\3.3_Original analysis [revised database]\Datasets*) and in **DEFINE_FUCRL_ROBUST.pdf** for the additional robustness analysis (location: CDROM subfolder *3_Datasets and Programs\3.4_Robustness analysis [revised database]\Datasets*).

CSLB Response Appendix 6C:

The requested data fields are located in dataset CRL_Q6BR in CDROM subfolder *Attachment 6\revised data robustness analysis* (see *CSLB Response 6*).

Reviewer Comment

Noted. It is unfortunate that the original BLA submission and 1st cycle amendments did not make clear that dataset variable fields whose defined names included "C1 INH" did not include either C1-INH given as blinded study medication or as emergency open label Berinert for laryngeal edema.

- In amendment 16 you state on p 6 in partial response to our request 4 of our August 21, 2008 fax that "In the concomitant medication dataset ADCM the variable TOANALG ("time of start of analgesics/anti-emetics/C1 INH/FFP" concomitant medication) is filled with the start date of the medication if the medication is on the list of analgesics/anti-emetics/C1 INH/FFP. In all other databases TOANALG contains the first start date of an analgesics/anti-emetics/…concomitant medication within a subject." Please clarify whether TTANA and TOANALG are intended to include data for masked rescue study medication (including placebo), as this is not clear from your definitions.

Sponsor's Response

CSLB Response Appendix 7:

As explained in *CSLB Response Appendix 6B*, TOANALG and TTANA are used only for the prohibited concomitant medications (i.e., analgesics/anti-emetics/open-label C1-INH or FFP documented on the "prior/concomitant medication" CRF). These variables include neither the blinded rescue study medication (Berinert or Placebo) nor the open-label emergency study medication (Berinert).

TOANALG is the time point of analgesics/anti-emetics/open-label C1-INH or FFP (i.e., absolute date/time), while TTANA is the time difference from start of blinded study medication to start of analgesics/anti-emetics/open-label C1-INH or FFP (in hours).

Reviewer Comment

Noted.

- In Amendment 17 submitted September 12, 2008, p 2 of "Guide to datasets and programs for additional analysis required by FDA fax dated 21August,2008," it states that:

  - "All programs and study specific macros used for the additional efficacy analysis of study CE1145_3001 can be found in "STATISTICAL\FDA_21Aug2009\PROGRAMS" and that "Data preparation programs were used to create new permanent analysis datasets available in the folder "STATISTICAL\FDA_21Aug2009\DATASETS\ANALYSIS."

  - "To obtain correct results the data preparation programs need to be used in the specified sequential order as indicated in the document "LIST_OF_PROGRAMS.PDF."

    Please be advised that "LIST_OF_PROGRAMS.PDF appears to be missing from the CD-ROM submitted as part of Amendment 17. Please supply this document.

Sponsor's Response

CSLB Response Appendix 8:

The **PROGRAMS subfolder** in Amendment 17 (submitted on 12 September 2008) that includes the file LIST_OF_PROGRAMS **was inadvertently not copied to the CDROM for that amendment. This PROGRAMS folder, including the file LIST_OF_PROGRAMS, is now provided in CDROM subfolder *Attachment Appendix 8\statistical\FDA_21Aug2008\programs*.**

Note: The subfolder structure from Amendment 17 ("statistical*FDA_21Aug2008\programs*") is retained for ease of identification.

Reviewer Comment

The sponsor's confirmation statement that the LIST_OF_PROGRAMS document and PROGRAMS folder was not included in Amendment 17 confirms, as previously stated in my original BLA review, that the sponsor did not provide during the initial review cycle the complete detailed methodology and fields the sponsor used to calculate the primary endpoint for the pivotal trial.

- We note that the variable "SGANAN" (SG [subgroup] with/without analgesics/anti-emit-num") was assigned a value of "'1' if at least one of cmexcl1a, cmexcl2, cmexcl3, --cmexcl10 = 'Y'" In the original submission concomitant medication dataset, ADCM, includes the following variables:

    - "CMEXCL1A" is defined as "C1-INH(+FFP) (4hrs)"
    - "CMEXCL2" is defined as "Anti-Emetics: Antihistamins [sic] (<4h),"
    - "CMEXCL3" is defined as "Anti-Emetics: Antidopaminergics (<4h)"
    - "CMEXCL4" is defined as, "Anti-Emetics: Benzodiazepines (<4h post)"
    - "CMEXCL5" is defined as "Anti-Emetics: Corticosteroid (<4h post),"
    - "CMEXCL6" is defined as Anti-Emetics: 5HT Recep. Antag. (<4h),
    - " CMEXCL7 is defined as, "Anti-Emetics: Miscellaneous (<4h),"
    - "CMEXCL8" is defined as "Anti-Cholinergics (<4h),"
    - "CMEXCL9" is defined as "Narcotic Pain Meds = Analgesics (<4h)," and
    - "CMEXCL10" is defined as "ACE Inhib. Within 4 Weeks Before Treat."

  It is not clear whether you have used derived variable SGANAN is analyses of the study's primary efficacy endpoint. Please clarify.

Sponsor's Response

CSLB Response Appendix 9:

The variable SGANAN (subgroups analgesics use) was derived if a prohibited medication (i.e., analgesic/anti-emetic/open-label C1-INH or FFP according to Appendix IVa of the SAP for final analysis, Version 2.0) was administered during the first 4 hours after ToS, but SGANAN was not used for analysis of the primary efficacy endpoint TtRel+.

The variable TOANALG is used for analysis of the primary efficacy endpoint TtRel+ (i.e., if TOANALG was less than or equal to ToSRel, then TtRel+ was set to poor/failure outcome of 24 hours).

Reviewer Comment

It is unfortunate that the sponsor's original BLA submission and 1st cycle amendments did not make clear that SGANAN and the related listed 10 "CMEXCL…" derived field variables were not used in the primary endpoint analysis.

- If you have used derived variable SGANAN in primary endpoint analyses, it appears you may not have properly followed the protocol and imputed values of 24 hours (or 4 hours in the case of analysis 1A requested in our fax information request dated August 21, 2008) for all subjects who received analgesics, anti-emetics, or "non-permitted" medications which may potentially

confound interpretation of the primary endpoint only if such medications were first administered prior to the subject's self-reported time to start of relief of HAE attack symptoms. Please comment.

Sponsor's Response

CSLB Response Appendix 10:

The variable SGANAN was not used for the analysis of the primary efficacy endpoint TtRel+ (see *CSLB Response Appendix 9*).

Reviewer Comment

Noted.

- It is not clear whether administration of any of the additional 4 classes of medications/medications "Non-permitted" by the protocol until after complete resolution of the HAE attack were taken into account in determining values of the derived variables CMEXCL1A and SGANAN. The additional 4 classes of "Non-permitted" medications/medications included:

  - Any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis
  - Attenuated androgens (for subjects not previously treated with androgens) or increased doses of androgens (for subjects already treated with androgens)
  - Tranexamic acid (for subjects not previously treated with tranexamic acid) or increased doses of androgens (for subjects already treated with tranexamic acid)
  - Aminocaproic acid (for subjects not previously treated with aminocaproic acid) or increased doses of androgens (for subjects already treated with aminocaproic acid)

Sponsor's Response

CSLB Response Appendix 11:

The additional 4 classes of "non-permitted" medications mentioned in *CBER Comment Appendix 11* did not lead to the imputation of a poor/failure outcome for the primary endpoint for the following reasons:

1. Approved or experimental drug targeting the biological mechanisms of action of C1-INH:
   No such medications were administered to any subject in the study (see *CSLB Response 5D*).
2. Attenuated androgens, tranexamic acid, and aminocaproic acid:
   CSLB's review of these medications has confirmed that all of these medications recorded as "ongoing" on the prior/concomitant medication CRF

   – had started with a documented dose regimen long before start of the study (i.e., at least several months) with no change in dosage

   or

- were administered outside of the 5-hour time window prior to start of study medication.

Therefore, none of these medications led to the imputation of a poor/failure outcome for the primary endpoint, neither for the original analysis nor for the additional robustness analysis (see *CSLB Response 5D*).

Reviewer Comment

Noted.

- Although Figure 11.2.1 states for Berinert 20 U/kg bw "N-43, censored – 5)," Figure 11.1.1 shows that 6 subjects in this high dose group were assigned [an imputed time] to initial relief of symptoms of 24 hours. Please explain this discrepancy.

Sponsor's Response

CSLB Response Appendix 12:

The discrepancy is due to Subject -b(6)- (Berinert 20 U/kg group) who received open-label Berinert as emergency study medication at 2:09 hours after ToS, which resulted in the imputation of a poor/failure outcome for the primary endpoint TtRel+ (Figure 11.1.1). As explained in *CSLB Response 14*, the subject was inadvertently not censored in Figure 11.2.1, but was included with the non-censored TtRel value of 4.65 hours. This also affects Table 11.17.3 and Statistical Appendix 16.1.9.4.1-3. Corrected Figure 11.2.1, Table 11.17.3 and Statistical Appendix 16.1.9.4.1-3 are located in CDROM subfolder *Attachment 14* (*Figure 11.2.1_new_original, Table 11.17.3_new_original,* dataset *CRL_Q14O*).

Reviewer Comment

Noted.

- We request you redo the primary endpoint analyses for the ITT population taking the following into account:

  - The protocol stated "Concomitant medications should be kept to a minimum during the study, especially during the acute attack. However, if these are considered necessary for the subject's welfare and will not interfere with the study medication/study endpoint, they may be administrated at the discretion of the investigator…Due to potential interference with assessment of the primary efficacy variable, the use of pain medication and anti-emetics is strongly discouraged during the acute phase of treatment. If possible, these medications should not be used until at least four hours after start of study medication administration. **Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received these types of medications listed in the CRF**."

    We note, however, that the use of discouraged and "non-permitted" (open-label C1-Inhibitor, fresh-frozen plasma, etc.) during the study was extensive. By our count, using the original submission ADCM concomitant medications database, at least 65 out

of 124 (>50%) of randomized subjects received "discouraged" or potentially "non-permitted" medications during the study.

In order to understand the impact of the administration of these concomitant medications on the study outcome measures, we need to know when these medications were administered in relation to variables such as ToSRel (time of initial relief of symptoms) "TTREL" (time of initial relief of symptoms minus time of administration of randomized CTM) and the derived data variable, "TTRELP" (also variously called TTREL+ and TtRel+ in your BLA and various amendment submissions, corresponding to TTREL, but set to a "poor/failure" imputed value of 24 hours in the case of subjects who received rescue study medication or open label CTM or analgesics or anti-emetics or FFP prior to TTREL).

Sponsor's Response

CSLB Response Appendix 13:

CSLB has performed this analysis (see *CSLB Responses 5A, 5C* and *10*) and provides an analysis dataset (CRL_Q6BR) that contains the times of use of "discouraged" and "non-permitted" medications as well as the time differences between administration of these medications and a) the start of study medication (ToS) and b) the start of relief (ToSRel). The results of the additional robustness analysis that takes into account these medications are presented in *CSLB Response 5C*.

Reviewer Comment

Noted.

- We request you also impute a "poor/failure" outcome of 24 or (or 4, depending on the analysis) hours for all subjects who received any of the 6 categories of medications/medications "Non-permitted" by the protocol (i.e., "any approved or experimental drug targeting the biological mechanisms of action of C1-INH such as modulation of components of the contact or complement system, coagulation, and fibrinolysis, fresh frozen plasma (FFP), attenuated androgens, tranexamic acid, or aminocaproic acid (for the latter 3 drug classes only if the subject was not previously treated with the drug or if previously treated but administered increased doses of the drug) either within 5 hours prior to the time of administration of randomized CTM or prior to TOSREL (time of start of relief of symptoms) or for whom the start date and/or time of such concomitant medications is missing.

Sponsor's Response

CSLB Response Appendix 14:

As explained in *CSLB Responses 5C and 6*, CSLB has performed the requested analysis and is providing a dataset that includes the reasons for imputation of a poor/failure outcome as well as the types and time points of non-permitted medications. This dataset is provided both for

- the original analysis based on the prohibited medication list from Appendix IVa in the SAP for

the final analysis, Version 2.0 (i.e., dataset CRL_Q6BO; location: CDROM subfolder *Attachment 6\revised data original analysis*), and

- the additional robustness analysis conducted in response to *CBER Comment 5C*, based on the medication list *PROHMED.xpt* (i.e., dataset CRL_Q6BR; location: CDROM subfolder *Attachment 6\revised data robustness analysis*).

Both datasets are also located in CDROM subfolders *3_Datasets and Programs\3.3_Original analysis (revised database)\Datasets* and *3_Datasets and Programs\3.4_Robustness analysis (revised database)\Datasets*). See *CSLB Response 5D* and *CSLB Response Appendix 11*.

Reviewer Comment

Noted.

- In amendment 16 you state on p 6 in partial response to our request 4 of our August 21, 2008 fax that "In the concomitant medication dataset ADCM the variable TOANALG (time of start of analgesics/anti-emetics/C1 INH/FFP concomitant medication) is filled with the start date of the medication if the medication is on the list of analgesics/anti-emetics/C1 INH/FFP. In all other databases TOANALG contains the first start date of an analgesics/anti-emetics/…concomitant medication within a subject."

  Your representative indicated during the teleconference held November 12, 2008 that the list of analgesics/anti-emetics/C1 INH/FFP" was contained in an appendix to the [revised] statistical analysis plan. Incidentally, we note that this list was not included in the original statistical analysis plan, but was submitted approximately 1 month before the last subject had completed the 7-9 day follow up visit of the study. Appendix IV: "Prohibited medications, Status October26, 2007" lists "Narcotic Pain Medications (Analgesics)" but does not include non-narcotic analgesics, such as non-steroidal anti-inflammatory agents (NSAIDs) or acetaminophen which could, for example confound the interpretation of the response of HAE attack symptoms of facial tightness, abdominal discomfort, etc.

  The protocol stated on p 21 under the heading "Pain medication and anti-emetics" "Subjects will be counted as non-responders regarding the analysis of the primary endpoint, if they have received these types of medications listed in the CRF." On p 35 of the protocol under section 7.3.1 (Analysis of efficacy – Primary efficacy criterion) it states that "Then the primary efficacy variable is defined as:

  (i) TtRel+ = 24 hours (poor/failure outcome), if
  - the subject has received rescue study medication before ToSRel was reached
  - the subject has received analgesics/anti-emetics before ToSRel was reached,

  -ToSRel – ToS > 24 hours,
  Or ToSRel cannot be determined because of missing values

  (iii) ToSRel – ToS, otherwise

[where ToS = Time of start of study treatment and
ToSRel – time of start of relief of symptoms]

We therefore request that you add non-narcotic analgesics, including NSAIDs and acetaminophen, to the list of "any rescue medication" that results in an imputation of a "poor/failure" value of 24 (or 4, as appropriate, depending on the analysis) hours for subjects who were administered such concomitant medication anytime from 5 hours prior to ToS (time of start of study treatment) until TOSREL (the time of start of relief of symptoms). Please redo and resubmit your primary endpoint analyses accordingly.

Sponsor's Response

CSLB Response Appendix 15:

CSLB has performed the requested analysis (additional, exploratory robustness analysis), incorporating all analgesics administered between 5 hours before study medication and ToSRel (see *CSLB Response 5C*). See *CSLB Responses 5A, 5B3b, and Appendix 7*.

Note: As previously stated, there is no basis in the protocol for the 5-hour time window before start of study medication.

The sentence "Subjects will be counted as non-responders regarding the analysis of the primary endpoint if they have received these types of medications listed in the CRF" (page 21 of the protocol) indicated that CSLB planned to include a list of prohibited medications in the CRF to define the prohibited medications resulting in a poor/failure imputation of 24 hours for the primary endpoint. As it was recognized that this list would be variable due to new drugs being administered during the course of study conduct, a list separate from the CRF was created and distributed to the investigators (date of list: 13 February 2006; see file *prohibited medication list for investigators* in CDROM subfolder *Attachment Appendix 15*). Therefore, this list was seen as a living document, to be updated with new drugs as they were administered in the course of study conduct. This list was first used in the SAP for the 1st interim analysis (Version 2.0 of 01 December 2006), and it was later updated with new drugs in the SAP for the final analysis (Version 2.0 of 26 October 2007) before unblinding of the study. Thus, the list of prohibited medications was not only generated for the final analysis, but had already been generated much earlier.

Please refer to the Cover Letter that provides CSLB's and outside consultants' position concerning the ineffectiveness of non-narcotic pain medications in the treatment of HAE attacks (location: CDROM subfolder *1_Cover Letter + Attachments A, B, C*). The individual letters from the outside consultants are also located in CDROM subfolder *Attachment 5C*.

Reviewer Comment

On p 35 of the protocol under section 7.3.1 (Analysis of efficacy – Primary efficacy criterion) it states that "Then the primary efficacy variable is defined as:

(i) TtRel+ = 24 hours (poor/failure outcome), if

- **the subject has received rescue study medication before ToSRel was reached**
- **the subject has received analgesics/anti-emetics before ToSRel was reached [emphasis added],**

-ToSRel – ToS > 24 hours,
Or ToSRel cannot be determined because of missing values

(iv) ToSRel – ToS, otherwise

[where ToS = Time of start of study treatment and
ToSRel – time of start of relief of symptoms]

As stated earlier, the sponsor has not provided data to indicated that non-narcotic analgesics may not at least partially mitigate some facial and/or abdominal HAE attack symptoms. Notwithstanding the sponsor's distribution of a list of prohibited medications to the investigators, it is appropriate, given the wording of the protocol, to emphasize the FDA requested "robustness" analysis of the primary endpoint which imputes a poor/failure value of 24 hours for subjects who received non-narcotic analgesics prior to ToS.

While it is true as the sponsor points out that the start of the time window for imputing a 24 hour value for subjects who analgesics/antiemetics and non-permitted medications prior to ToSRel was not stated in the protocol, it is clear that if such medications are taken prior to ToS but have their peak blood/tissue level and peak pharmacodynamic effect following ToS, this would confound the interpretation of efficacy. Given that the duration of action of many of the analgesics/anti-emetics and non-permitted medications is on the order of 6 hours, a 5 hour time window prior to ToS was chosen as the starting time for the window of interest, as it seems that if such medications were taken earlier than this time, their pharmacodynamic peak would likely occur prior to ToS and not interfere with efficacy assessment. Note that the sponsor has not proposed an alternative starting time for the time window of interest.

Letter-ready comments communicated to the sponsor by telecon and fax dated 29 May 2009, based on amendment 25, together with sponsor responses in Amendment 31 dated 22 July 2009, and reviewer comments on sponsor responses:

[Note: CBER provided by email on 26 June 2009, at the sponsor request made by email on 22 June 2009, clarifications to questions 1, 8, and 9 above.]

1. We reiterate our request #6 from our Complete Review letter to you to "Please provide a single analysis database that contains all raw data and derived data fields needed to completely validate your primary efficacy endpoint of time to initial relief of symptoms." Your amendment 25 states that either 2 or 4 databases must be used to reproduce the primary endpoint analyses. Please ensure in the to-be-submitted database that all variables

have a single consistent definition. We note that in your previously submitted databases, some variables' definitions vary according to the database in which they are found.

Sponsor Response:

Based on clarification from CBER regarding the database structure (received via email on 29 June 2009), CSLB is providing the required database CRL_Q6CN with all raw data and derived data fields needed to completely validate the primary efficacy endpoint (i.e., time to onset of symptom relief). This new database is provided in CDROM subfolder Attachment 1_Clinical/Question 01. In addition, this CDROM subfolder contains the following files:

- *DEFINE.pdf for database CRL_Q6CN*
- *Examples for data retrieval.doc: A guidance document with examples of data retrieval via (b(4)) SQL queries for key validation topics (as discussed in the 09 July 2009 web conference with CBER).*

Reviewer Comment:

Noted.

2. You state under the 2nd bullet on p 10 of 14 in your "Reviewer Guide to the Database" submitted with amendment 25, "If the subject was asleep at a certain point and confirmed symptom relief after awakening (variable EFIMPROV), the time point of symptom relief onset was defined as the first time of the last period of sleep before symptom relief." Please clarify the meaning of this statement.

Sponsor Response:

In response to CBER's request, CSLB provided a written clarification on 07 July 2009 and discussed with CBER representatives during a web conference on 09 July 2009. During that discussion, CBER stated that CSLB's response to this request was adequate and had no further questions.

a period of time starting before ToS and ending after ToS (before or after ToSRel), TtRel+ was not imputed with the poor/failure outcome of 24 hours if there was an investigator comment confirming that the medication was not administered during the following time periods:

- between ToS and TtRel [sic?] for the original analysis
- between 5 hours before ToS to ToSRel for non-narcotic pain medication and ToS to ToSRel for all other medications in the list for the **additional robustness analysis (*PROHMED.xpt)*.**

This appears to conflict with the statement on p 13 of 14 of this document which states:

> For the additional robustness analysis conducted in response to CBER's Comment 5C, the following additional derivation criteria need to be taken into account to complete step 2 (additional variables DATACOM, EXCLTEXT, EXCLRES, HAEDIFF, HAEDIFFH):

- The extended time window for prohibited medication use, i.e., from 5 hours before start of study medication to onset of symptom relief.
- Administration of any of the prohibited concomitant medications on the list for the additional robustness analysis ((*PROHMED.xpt) in this extended time window.*

Please clarify which of the above statements is correct. If the former is correct, please redo and resubmit the primary endpoint robustness analysis that uses the extended time window of from 5 hours prior to administration of blinded study medication until ToSRel, as requested in our CR letter.

Please also clarify how and why the variables, HAEDIFF and HAEDIFFH [variables containing the time between the estimated ***start*** of attack under study and the event in EVENT] were used for step 2 of the "robustness" analysis submitted in amendment 25 in response to the CR letter.

Sponsor Response:

The information on page 8 of the "Reviewer Guide to the Database" was incomplete. However, it is correct that the extended time window (i.e. -5 hours to onset of relief) was indeed used for all prohibited/discouraged medication in the additional robustness analysis. This is described in detail on pages 11 to 13 of the "Reviewer Guide to the Database" (Section 4, subsection "Step 2: Imputation of Poor/Failure Outcome of 24 hours").

As described above, the exclusion criteria concerning non-permitted medication (specifically narcotic pain medication and anti-emetics) required that the subject did not receive these medications between start of the HAE attack and start of the study medication. For the robustness analysis, the requirements were that the administration of non-permitted medications within 5 h before start of blinded study medication led to imputation of a poor/failure outcome of 24 h for the primary endpoint.

The variables HAEDIFF and HAEDIFFH were added to the dataset because they are used to verify if the start of study medication took place >5 h after the start of attack. If administration of study medication was started >5 h after start of attack, it can be assumed that - in combination with the exclusion criteria - narcotic pain medication and anti-emetics were not administered within the 5-h time window required for the robustness analysis.

Reviewer Comment:

Noted. However, it was clearly stated by FDA in the CR letter that, in cases where investigator query forms conflict with hospital medication records, the latter are to be used in the FDA-requested "robustness" analysis. In like vein, if the hospital medication records appear to conflict with the investigator's checkmark indicating "no" next to exclusion criterion #15 concerning use by the subject of narcotic pain medication and/or anti-emetics following the start of the HAE attack, the FDA analysis will use the hospital medication records to resolve apparent inconsistencies in the data.

The phrase "first time of the last period of sleep before symptom relief" in the "Reviewer Guide to the Database" was intended to signify that, in case of several periods of sleep, only the period after which the relief was confirmed for the first time was relevant for this calculation.

There were a total of 7 subjects (Placebo: 1 subject [No. (b)(6)]; Berinert 10 U/kg: 4 subjects [Nos. (b)(6)]; Berinert 20 U/kg: 2 subjects [Nos. (b)(6), (b)(6)]) who confirmed relief after awakening. The time of start of relief was set to the first scheduled time point during sleep for 6 of the 7 subjects. The seventh subject, Subject No. (b)(6), had stated relief for the first time already at the last scheduled time point before sleep (30 min), and relief was confirmed at the first time point after sleep (1 h), so that the rule for consecutive time points in case of missing assessments applies:

"In case of missing assessments of the relief or violations of the time schedule the minimal conditions for two time points to be considered as consecutive are to lie within,

1 hour at the most	during the first 4 hours
2 hours at the most	from 4 to 8 hours and
6 hours at the most	from 8 hours to 24 hours."

(SAP versions 1.0 and 2.0, Chapter 3.1.3)

The determination of ToSRel for each of the 7 subjects who confirmed relief after awakening is provided below (information from database CRL_Q6a; NOTE: Subjects (b)(6) received rescue study medication prior to ToSRel. Thus, time to onset of relief [primary endpoint, TtRel+] was imputed to the poor/failure outcome of 24 hours):

1. Subject (b)(6) (Placebo):

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
1 H	03JUN2006	6:05	N
1 H 15 MIN	03JUN2006	**6:20**	Subject asleep
1 H 30 MIN	03JUN2006	6:35	Subject asleep
1 H 45 MIN	03JUN2006	6:50	Subject asleep
2 H	03JUN2006	7:05	Y

ToS=5:05, ToSRel= 6:20, TtRel = 1.25 h

2. Subject (b)(6) (Berinert 10 U/kg):

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
1 H 30 MIN	07SEP2006	15:50	N
1 H 45 MIN	07SEP2006	**16:05**	Subject asleep
2 H	07SEP2006	16:20	Y

ToS= 14:20, ToSRel=16:05 h, TtRel = 1.75 h

3. Subject (b)(6) (Berinert 10 U/kg):

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
15 MIN	24SEP07	2:26	N (no relief)
30 MIN	24SEP07	**2:41**	subject asleep
45 MIN	24SEP07	2:56	subject asleep
1 H	24SEP07	3:12	Y (onset of relief confirmed)

According to the rule above, the time of onset of relief (ToSRel) is defined as the actual time of the 30-minute visit after infusion, i.e. at ToSRel=2:41 (ToS= 2:11, TtRel = 0.5 h).

4. Subject (b)(6) (Berinert 10 U/kg):

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
1 H 15 MIN	28JUN2006	14:00	N
1 H 30 MIN	28JUN2006	**14:15**	Subject asleep
1 H 45 MIN	28JUN2006	14:30	Subject asleep
2 H	28JUN2006	14:45	Y

ToS= 12:38, ToSRel=14:15, TtRel = 1.62 h

5. Subject (b)(6) (Berinert 10 U/kg)

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
15 MIN RES (after rescue study medication)	07DEC2006	1:55	N
30 MIN RES	07DEC2006	**2:10**	Subject asleep
45 MIN RES	07DEC2006	2:25	Subject asleep
1 H RES	07DEC2006	2:40	Y

ToS= 06Dec2006, 21:10; ToSRel=2:10, TtRel = 5 h

6. Subject (b)(6) (Berinert 20 U/kg)

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)
2 H RES (after rescue study medication)	27AUG2007	13:19	N
2 H 30 MIN RES	27AUG2007	**13:49**	Subject asleep
3 H RES	27AUG2007	14:19	Y
2 H RES (after Study Rescue Medication)	27AUG2007	13:19	N

ToSRel= 13:49, TtRel = 4.65 h, ToS=9:10

7. Subject (b)(6) (Berinert 20 U/kg)

Scheduled time point (Variable VISIT)	Date of assessment (Variable EFDI)	Time of assessment (Variable EFTI)	Subject's answer to question 1 (regarding onset of relief) (Variable EFIMPROV)	Start of improvement (actual time as indicated by the subject) (Variable EFIMPTI)
30 MIN	17APR2007	17:32	Y	**17:30**
45 MIN	17APR2007	17:50	Subject asleep	
1 H	17APR2007	18:05	Y	17:30

In this subject, ToSRel is 17:30, i.e., the actual time of improvement EFIMPTI, documented during the assessment at 17:32 (variable EFTI) (ToS= 17:01, TtRel = 0.4833 h).

Reviewer Comment:

Noted. The sponsor's calculation of TtRel for these 7 subjects appears to be appropriate.

1. On p 8 of 14 of the "Reviewer Guide to the Database" submitted with amendment 25, you state:

In case prohibited/discouraged concomitant medication according to the respective list…*PROHMED.xpt* [i.e., the list for the additional robustness analysis conducted to address CBER's *Comment 5C*]) was administered over

3. Please clarify what values were imputed for variables HELPE AND HELLPTI in instances where CRF values for both CMONGO and CMENDTF were missing.

Sponsor Response:

No imputation was performed for either HELPE and/or HELPTI for the following reasons:

(i) For subjects receiving concomitant medication, there is no subject where CMONGO and CMENDTF are both missing; thus there was no need for any imputation of either HELPE and/or HELPTI.

(ii) For subjects not receiving any concomitant medication (indicated by NONE='None'), all related variables (including HELPE and/or HELPTI) are missing by definition.

Reviewer Comment:

Noted.

4. You state in part in response to our CR letter item 5D that narcotic pain medications only resulted in imputation of a poor/failure outcome of the primary endpoint "If they were administered in the critical time period between start of randomized study medication and start of symptom relief, or 24 hours after start of randomized study medication." Please clarify when a poor/failure was imputed if these medications were administered "between start of randomized study medication and start of symptom relief" vs. if they were administered between start of randomized study medication and 24 hours.

Sponsor Response:

In case TtRel was not missing and <24 hours, TtRel was imputed to the poor/failure outcome of 24 hours if subjects received the prohibited/discouraged medications between start of randomized study medication and onset of symptom relief.

For TtRel missing or >24 hours, there was the following additional rule:
If TtRel was missing or >24 hours, it resulted in imputation of a poor/failure outcome of the primary endpoint if narcotic pain medications were administered between start of randomized study medication and 24 hours. Note: For subjects with missing TtRel or TtRel >24 hours, TtRel was to be imputed with the 24 hour poor/failure outcome anyway. There were 4 subjects with missing TtRel values, but no subjects with TtRel values >24 hours.

Reviewer Comment:

It is noted that 4 subjects in the trial had missing TtRel values for the primary endpoint, and were therefore imputed to have "poor/failure" values of 24 hours.

5. You state in response to CBER CR letter item 14 that subject -b(6)-, who was randomized to the Berinert 20 U/kg group, received open-label emergency study medication at 1.09 hours after the start of randomized, blinded study medication. This conflicts with your

statement in response to CBER CR letter item 11 that each of the 11 subjects in the study who received C1-INH as open-label concomitant medication had documented start dates for concomitant open-label C1-INH that were "At least 2.5 days after administration of randomized study medication, and "Always after time of start of relief." Further, in your response to item 11, subject -b(6)- is not listed among the 11 subjects who received C1-INH as open-label concomitant medication. Please clarify.

Sponsor Response:

The response in Item 14 states that Subject -b(6)- received open-label emergency study medication at 2.09 hours after start of randomization. The 11 subjects who are discussed in Item 11 received open-label concomitant medication. Open-label emergency study medication was not documented as concomitant medication but as study medication*.

*Exception: For Subject -b(6)- (Berinert 20 U/kg group), the open-label emergency study medication given more than 13 days after randomized, blinded study medication is also documented as concomitant medication.

Reviewer Comment:

The sponsor has been inconsistent in when it has classified use of Berinert as a concomitant medication vs. when it has been considered as study medication. Subject -b(6)- **should be considered a treatment failure if TtRel is > 2.09 hours.**

6. By our count, a total of 55 subjects are listed in your QRL_Q6C database submitted with amendment 25 in which you indicated in the field named RIMPUTE that you have imputed the value for the primary endpoint, time to initial relief of symptoms. Yet, in the primary endpoint field named RTTRELP, only 4 subjects have an imputed value of 24 hours. The remaining 51 subjects for whom you indicated you have imputed a primary endpoint "failure" value have a dot as the field entry. Please clarify. We note the 4 subjects with a 24 hour imputed value for RTRELP have missing data for time of initial relief variable, ToSRel. The remaining 51 subjects have values in the RIMPREAS (Reason for imputation (robust)) field corresponding to "Prohibited med. Given before time to onset of relief" or "Blinded rescue med. Given before time to onset of relief."

Sponsor Response:

A total of 57 subjects have an imputed value for the primary endpoint (see also *Listing_Q9_24hour_poor_failure_endpoint_robustness* submitted with Amendment 25 on 08 April 2009). Selecting the records in the dataset QRL_Q6C with RIMPUTE = "yes" results in a list of all reasons for imputation of the primary endpoint for these 57 subjects in the robustness analysis. A selection of records with RTTRELP=24 will also yield a list of the 57 subjects with the primary endpoint set to 24 h. In the original analysis performed on the revised database, a total of 34 subjects have an imputed primary endpoint (IMPUTE="yes"). A single subject can have multiple reasons for imputation.

Four subjects (---b(6)----------) show an imputed primary endpoint value in the variable RTTRELP variable when RIMPUTE="yes" is used as selection criterion (the same applies to TTRELP and IMPUTE for the original analysis). This is because the reason for the subject's endpoint imputation is the missing time to start of relief (TTREL) itself. The remaining 53 subjects have reasons for imputation of the primary endpoint other than missing TTREL.

The time to onset of relief and the imputed value for time to onset of relief can be found in the variables TTREL (RTTREL for the robustness analysis) and TTRELP (RTTRELP for the robustness analysis), respectively. However, the values are stored only once per subject in the record where EVENT="Onset of relief of symptoms".

The new dataset QRL_Q6CN is organized in a "vertical" data structure, with multiple records per subject representing the study events that are relevant to the imputation of the primary endpoint (study medication, concomitant medications, time to start of relief, ...) in chronological order. To enable an easier selection of all subjects with imputed primary endpoint values, a new flag on the subject level is introduced in the new dataset CRL_Q6CN (see CBER Comment 11). The following new variables are set to "yes" if at least 1 reason for imputation of the primary endpoint for this particular subject applies:

SUBIMPUT = "yes" - subject with imputed endpoint – original analysis.
RSUBIMPU = "yes" - subject with imputed endpoint – robustness analysis.
R2SUBIMP = "yes" - subject with imputed endpoint – R2 analysis.

Reviewer Comment:

Noted. The sponsor's response appears inconsistent, in that it states "Selecting the records in the dataset QRL_Q6C with RIMPUTE = "yes" results in a list of <u>all</u> reasons for imputation of the primary endpoint for these 57 subjects in the robustness analysis. A selection of records with RTTRELP=24 will also yield a list of the 57 subjects with the primary endpoint set to 24 h" and yet also states "Four subjects (---b(6)----------) show an imputed primary endpoint value in the variable RTTRELP variable when RIMPUTE="yes" is used as selection criterion (the same applies to TTRELP and IMPUTE for the original analysis)." FDA employed the new combined database (and a review of supporting concomitant medication source documents/copies of hospital medication records) for its primary endpoint analysis.

7. You state in response to CBER CR letter item 10 that "Hospital records/source data to confirm the actual times of administration were collected from all subjects who, between 5 hours before and 24 hours after start of randomized study medication, received any of the concomitant medications included in the list *PROHMED.xpt* for the additional robustness analysis." We understand this list to include "any rescue medication" (including all "discouraged" (narcotic and non-narcotic analgesics and antiemetics) and all 6 classes of "Non-permitted" medications) being taken prior to study start and where such medication was recorded as "ongoing" or for which the stop date was missing. In cases where the investigator's response to your query concerning whether such medications were taken

during the critical part of the study conflicts with the hospital medication record, it was our intent that you use the latter data rather than the investigators' responses to your query sheets to construct your revised databases and analyses. Please revise your databases and analyses submitted in your complete response to our CR letter accordingly if you did [not] use the hospital medication records in cases where they conflicted with the investigators' responses to your query sheets.

Sponsor Response:

All conflicts between the hospital records and the investigator comments (i.e., answer to queries for the primary analysis) were resolved in the procedure of hospital record review. The information in hospital records overruled the investigator comments in case of conflicting information. Thus, CSLB believes that the analysis was performed according to CBER's requirements and that no new analysis is necessary.

Reviewer Comment:

Noted. However, this reviewer has discovered errors in Table Listing Q5B3b, "Prohibited/discouraged concomitant medication according to PROHMED including classification and time between start of blinded study medication and start of concomitant medication," submitted in Amendment 25. For example IV Demerol was given on the day study medication was administered according to submitted source documents for subject -b(6)-**, but this narcotic concomitant medication is not listed in Listing Q5B3b. In addition, for subject** -b(6)-**, who took the anti-emetic hydroxyzine 1.25 hours prior to receiving randomized study medication, the sponsor wrote in Listing Q5B3b that narcotic analgesics and anti-emetics had not been taken between start of attack and ToS. For subject** -b(6)-**, source documents show Demerol was given after onset of attack (but > 5 hour prior to ToS), yet the sponsor incorrectly wrote in Listing Q5B3b that narcotic analgesics and anti-emetics had not been taken between start of attack and ToS.**

8. Please submit a revised draft package insert at this time that takes into account the edits sent to you in 2008. The CLINICAL STUDIES section should provide a Kaplan-Meier curve for the robustness analysis based on imputation of a > 4 hour value for any subject who took any of the "discouraged" or "forbidden" medications (including non-narcotic analgesics) anytime between 5 hours prior to ToS and ToSRel. You may also include (below the results of the above analysis) the results of the same analysis, except that > 4 hour values are not imputed solely because a subject was documented to have received a non-narcotic pain medication between 5 hours prior to ToS and ToSRel. Please submit the results and methodology for the latter analysis, which we shall designate as the "R2 analysis."

Sponsor Response:

The requested Kaplan-Meier curves that address CBER's comments made during the 16 July 2009 conference call are provided in CDROM subfolder Attachment 2_Labeling/Supporting Information Package Insert. The source data tables for Package Insert Tables 1, 2, 4, and 8 to 12 are also

provided in this attachment (Note: For Package Insert Table 10, the percentages of subjects with relief within 4 hours in the abdominal and facial subgroups need to be calculated using the total number of subjects of the respective subgroup as the denominator, for example, in the abdominal subgroup: 29 out of 33 Placebo subjects [87.9%] and 33 out of 34 Berinert 20 U/kg subjects [97.1%]; see file Source Data Tables for Package Insert.pdf, page 21).

The R2 analysis was performed on the revised database (submitted with Amendment 25 on 08 April 2009) and is based on the robustness analysis ("Reviewer Guide to the Database", pages 10 to 13, section "Step 2: Imputation of Poor/Failure Outcome of 24 hours"). The only difference between the R2 analysis and the robustness analysis is the exclusion of the non-narcotic pain medication from the list of prohibited medication (PROHMED.xpt) for the R2 analysis.

The results of the R2 analysis are included in the newly created dataset CRL_Q6CN. The values for the imputed primary endpoint derived from the R2 analysis can be found in the variable R2TTRELP and can be compared to the results from the robustness analysis in variable RTTRELP. The medication classification used for the R2 analysis can be found in the variable RCAT. For the R2 analysis, concomitant medications with RCAT = "mild analgesics" were not taken into account for imputation of a poor/failure outcome of the primary endpoint.

Reviewer Comment:

Noted.

9. Please reference the specific amendment in which you explain in narrative fashion as well as using -b(4)- code, exactly how you calculated the primary endpoint. Your response to the CR letter does not provide this information in a stand alone statement, but rather references the original BLA submission and amendments without being specific as to location. Please submit a flow diagram, similar to the one on p 14 of 14 of the "REVIEWER GUIDE TO THE DATABASE," that details the methodology used to perform the "robustness" and "R2" analyses.

Sponsor Response:

CSLB did not provide a "stand alone narrative" describing the calculation of the primary endpoint in any submission prior to Amendment 25. In Amendment 25, such a narrative description for the validation/calculation of the primary endpoint was provided in Section 4 of the "Reviewer Guide to the Database".

The requested flow diagrams and -b(4)- programs for the original, robustness and R2 analyses are provided in CDROM subfolder *Attachment 1_Clinical/Question 10*. The following -b(4)- programs were used for calculation of the primary endpoint:

Program Name	Description
DEFF.- b(4)-	Define ToSRel, TtRel and the primary endpoint TtRel+, and additional efficacy variables
DADCMSEL_ORIGINAL.b(4)	Create flags for concomitant medication allowed/not allowed by protocol and create ToAnalg according to SAP 2.0, App. IVa
DADCMSEL_ROBUST. b(4)	Create flags for concomitant medication allowed/not allowed by protocol and create ToAnalg according to *PROHMED.xpt* list (including non-narcotic pain medication)
DADCMSEL_R2. b(4)	Create flags for concomitant medication allowed/not allowed by protocol and create ToAnalg according to *PROHMED.xpt* list (excluding non-narcotic pain medication)

Reviewer Comment:

Section 4 of the "Reviewer Guide to the Database" is not sufficiently detailed to readily permit validation of the sponsor's primary endpoint analysis. For example dataset variable names are not provided to permit identification of each time of administration of concomitant medications between t-5 hours and ToS. Nor are variable names provided that permit one to verify the sponsor's claim that the dose of androgens, aminocaproic acid, and tranexamic acid did not change within-subject during the time of trial participation. [Resolution of this deficiency required review of submitted SDs.]

10. Please redo and resubmit database QRL_Q6C with corresponding fieldnames from the robustness and R2 analyses side by side.

Sponsor Response:

CSLB has redone database QRL_Q6C as requested. This new database QRL_Q6CN is provided in CDROM subfolder *Attachment 1_Clinical/Question 01*.

Reviewer Comment:

Noted.

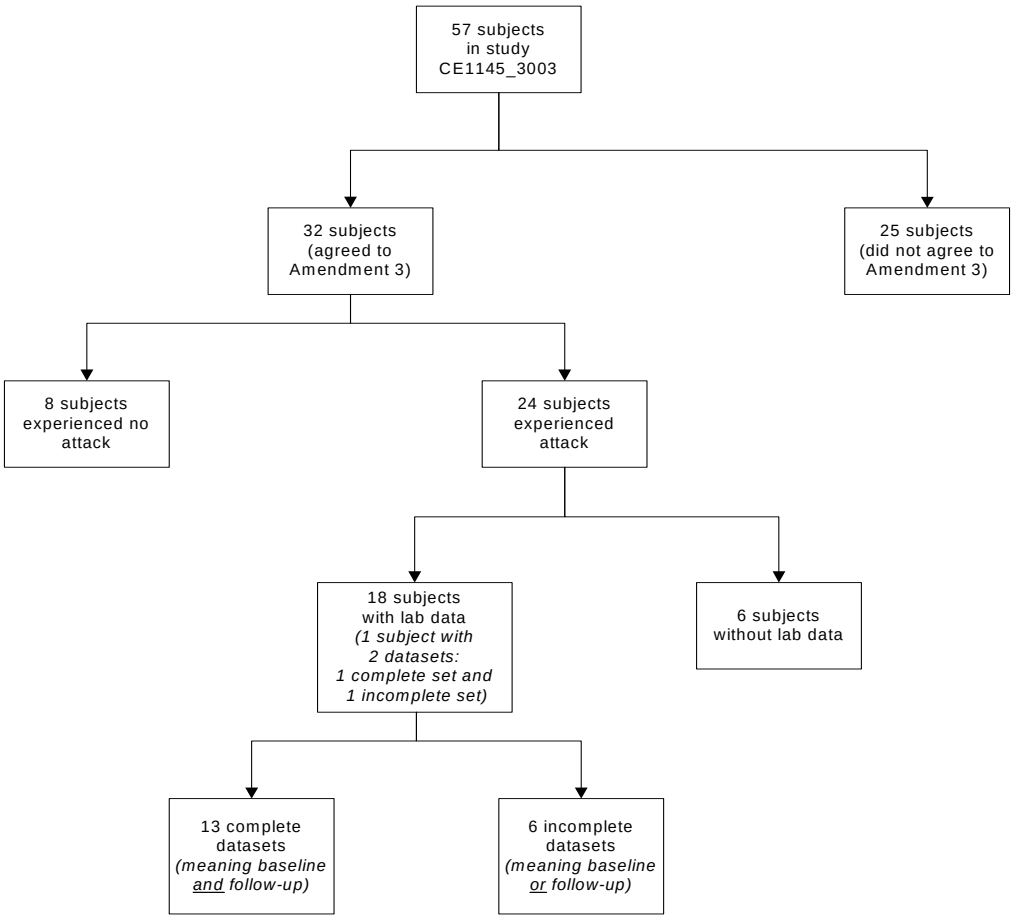
2nd Information Request Items based on Amendment 25 (mid-cycle comments from 2nd review cycle conveyed to sponsor) with sponsor responses in italics from Amendment 31 and reviewer comments in bold.

1. Item 19 from our Complete Review letter read "Please submit data from at least 40 subjects for routine chemistry, including renal and liver function and aminotransferases, hematology, and urinalysis, including microscopic examination of urine sediment, from following single and multiple dose exposure to the product and compare these to baseline

values." You have requested to submit these data in the form of the final study report for open-label extension study CE1145_3003 (I.M.P.A.C.T. 2), currently scheduled for December 2010, as a post-marketing commitment. Please submit interim data at this time in response to this request.

SPONSOR RESPONSE FROM AMENDMENT 31:

B. Local laboratory data from Extension Study CE1145_3003:
The flowchart below explains the disposition of the 18 subjects for whom CSLB can provide laboratory data based on Protocol Amendment 3, which implemented collection of local laboratory safety data. These data are provided in CDROM subfolder *Attachment 3_Additional information*.
Note: These are unclean data from an open database with a cut-off date of 15 July 2009.



Reviewer Comment:

The sponsor provided data tabulations of clinical chemistry, hematology (CBC and differential with platelet count) and urinalysis (with microscopic exam of sediment, but often not done) for 18 subjects from the ongoing open-label extension study. The following are among the abnormal lab values noted during review of these data:

Subject	Date from ToS	Analyte	Value
-b(6)-	**Day 515**	**AST**	**94**
-b(6)-	**Day 515**	**ALT**	**114**
-b(6)-	**Day 595**	**AST**	**32**
-b(6)-	**Day 595**	**AST**	**36**
-b(6)-	**Day 676**	**Eos**	**8%**
-b(6)-	**Day 714**	**Eos**	**11%**
-b(6)-	**Day 714**	**WBC**	**12.9 K**
-b(6)-	**Day 819**	**WBC**	**14.4K**
-b(6)-	**Day 836**	**WBC**	**3.7K**
-b(6)-	**Day 692**	**WBC**	**16.8K**

The elevated AST and ALT values in subject -b(6)- normalized. Urinalysis abnormalities, including pyuria, were rather frequent, but are not summarized in the above table as no clear pattern was evident.

2. Please provide copies of the correspondence with investigators concerning the list of discouraged and "non-permitted" medications that were considered to be in classes that could potentially confound the efficacy evaluation as it lengthened during the trial.

A. Prohibited medication list:
During the 09 July 2009 web conference, CBER requested to receive information on how CSLB provided updated prohibited medication information to the investigators (e.g. provide a copy of the cover letters). CSLB's study monitors provided the initial information during a monitoring visit. This original list was used in the SAP Version 2.0 for the interim analysis.

The updated list was used in the SAP Version 2.0 for the final analysis. This occurred 1 month after the study was closed for subject enrollment and no subjects were treated afterwards. Therefore, there was no need to provide this updated list to investigators.

Reviewer Comment on Additional Information from Amendment 31:

An incomplete list of specific drugs considered by the sponsor to be narcotic analgesics or anti-emetics was available to the investigators starting from the time of a monitoring visit whose timing is unclear and not stated by the sponsor. This list was used for the [initial] interim analysis, so it is possible that investigators may not have received this list until the study was well underway. Thus, many investigator may not have cautioned potential subjects for the study to avoid taking analgesics or anti-emetics at or near the onset of attacks, which is the custom for many/most of established HAE patients, as is evident from perusal of provided source documents for concomitant medications. Therefore, in the FDA sensitivity analysis for the FDA robustness analysis, all subjects for whom non-permitted or discouraged medications (in the Prohmed list) were marked as "ongoing" and/or for whom no stop date prior to the study was provided, a "poor/failure" value of 24 hours will be imputed for the primary endpoint unless other source documents establish that the medications in question were not taken between 5 hours prior to ToS and TosRel.

3. Please define the abbreviation, "SDV finding" in table Q5B3b.

The sponsor did not answer this question directly in writing, but confirmed by telephone that this refers to a "manual" review of source documents. The sponsor submitted a revised Table Q5B3b to make this clearer, but the sponsor stated during a teleconference that no other changes were made to the data from the original table, so the revised Listing was not reviewed.

REVIEW APPENDIX 1

Selected data abstracted from submitted source documents for individual subjects

Subject -b(6)- Randomization/Enrollment Source Documentation lists Zyrtec 10 mg prn. Attack onset was 28 Sept 2006 at 7:15. Tos was 11:03 on 3 Apr 2006 according to printed date, but no handwritten date. Source record states subject had used Berinert at home in the past. Pt also has felt that p.o. prednisone has stoped attacks in the past. At follow-up after participation, patient asked "Are you sure I got the drug?" Subject's abdominal pain worsened after discharge after dinner. No concomitant meds taken at follow-up visit.

For subject -b(6)-, Danazol 400 mg QD ("Patient Details.." sheet)was changed to Danazol 800 mg QD (randomization/enrollment sheet).

Source records for subject -b(6)- submitted in amendment 36 show on the "Concomitant Medication – Source Data HelpSheet" Danazol 400 mg PO QD with a stop date of 20 Nov 2007 and Cetor 1 g IV 2x per week (for prophylaxis) started 29 Oct 2007 with a stop date of 30 Dec 2007 and a note that "source docs indicate Cetor (C1 Esterase Inhibitor Concentrate, Sanquin) given > 1 month post study medication." Pt asked to come to hospital for facial attack. Another undated document lists both Danazol 400 mg QD and Lexapro (an SSRI anti-depressant) 5 mg QD (for anxiety) started Aug 2007 as current and previous concomitant meds. The stop date for Lexapro was listed as 20 Nov 2007. This subject's ToS was 23 Sept 2007 at 17:32.

Subject -b(6)-on Randomization/Enrollment form and on Current Drug Therapy sheet had listed oxandrolone 2.5 mg po qd since 2004 and Paxil 20 mg po qd since 2003. No medication records covering the period -5 hours to ToS were submitted.

Subject -b(6)- signed consent on 10 Oct and 25 Oct 2005 at 8:36. Pt had attack involving abdomen, face, and feet. Exclusion criterion box 15 checked.Concomitant medication sheet dated 16 Jan 2006 listed only Tylenol PM 2 tabsbs po x 1 on 15 Jan 2006 at 22:30. A different undated Concomitant Medications sheet lists 2 additional medicines, including Zelnorm for irritable bowel 6 mg po prn started unknown date, no stop date, but continued post-trial box not checked. A note to the file dated 2 May

2006 stated subject discharged 1 hour after rescue to resolution of all symptoms as of 30 min post rescue. No medication records clearly identified from -5 hours to ToS were submitted.

Subject -b(6)- signed consent 1 Dec 2005 on the day randomization requested at 12:20 for an abdominal attack. Exclusion criterion box 15 checked. Concomitant med list states "no new meds, "but screening med sheet not provided. Primary endpoint question for 3.5 hours has both no and yes with an x marked with initials by the no, as well as subject asleep crossed out and checked. Four hour time point primary endpoint question not answered. Rescue drug given marked between 4 and 5 hours. Attack began 1 Dec 2005 at 7:45 and became moderate or severe at the same time. Concomitant med sheet is undated, but has a note at the bottom dated 13 Jan 2006 stating subject was not on Ritalin in reference to ADR. This sheet lists Dicyclomine for cramping/nausea 20 mg q 4-6 h started 2004, stopped 11 Oct 2005, Allegra stopped 9/05, Promethazine 25 mg q 9 hrs prn starting pre-trial with no stop date and also a unitialed undated crossout stating stopped Nov 2005, and Vicoden q 8 hrs prn for otitis media stopped 29 Nov 2005.

Subject -b(6)- consent dated 26 Feb 2006. Concomitant med SD lists Loratidine prn begun pre-trial with a stop date of September unk 2005. Exclusion criterion 15 box checked. Randomization requested 26 Feb 2006 at 18:58.

Subject -b(6)- consented to be hospitalized on 27 June 2006. She had onset of facial edemam mild to severe, at 4 AM. She had had lower limb edema since 10 PM the night before. She also had abdominal discomfort. She had complete relief of symptoms on 28 June 2006 at 12:30 AM (translation). Rescue medication was administered but the time and date was not stated. Hospital discharge from ------- b(4)---------- occurred on 27 June at 15:15 (4 hours following last administration of investigational medication) and following significant improvement. Pt had abdominal and foot attack and probably by inference, facial attack, but this is unclear. Her discharge diagnoses included acugte facial and foot edema and C1 inhibitor deficiency. The patient had mild spasms, but the time of this symptom was not indicated. Pt also took BP meds plus Ezacyl at randomization and on discharge. "At hour 12 PM 4 PM, 8 PM, and 12 AM, the patient improperly evaluated the improvement – she did not make a comparison with her condition before the administration of the medicine." [Reviewer comment: This misunderstanding highlights the pitfalls of subjective patient-reported outcome measures.] Exclusion criterion #15 is checked, corresponding to No. Concomitant meds are listed as Exacyl (tranexamic acid) 3 x 1 po od 02.2006, Lokren (betaxolol) 20 1 x ¼ po od 03.2006 for htn, and Tetrtensif SR (Indapamidium – a diuretic) 1 x 1 po od 0-1.2005 27.06.06 and from ~ 2004 and Hepavax 3.

Subject -b(6)- signed consent 18 June 2007. Randomization requested that day at 10:15. Exclusion criterion 15 box checked no. Concomitant meds include Allegra (fexafeindine) qd, ASA 81 mg qd, and Aleve prn, all started pre-trial and none

bearing stop dates, although continued post-trial not checked. Subject discharged 19 June 2007 at 17:00. "Pt stated no meds other than routine taken 5 hours prior and 24 hours post" in signed but undated note that must have been written after Dec 2008 after FDA informed the sponsor of this time frame of interest. No SD clearly covering meds that may have been given other than study drug from -5 hours to discharge submitted.

Subject -b(6)- signed consent 12 Aug 2007 at 9:35. Date of randomization crossed out and initialed. Box 15 of Exclusion criteria checked. Concomitant med sheet is undated and lists Danazol for HAE 200 mg po qd and Lexapro (escitalopram, a SSRI) for depression, both with no end date and begun pre-trial. Another undated med sheet states just "No new."

Subject -b(6)-diary card lists Tylenol, Demerol, and Sudafed/Benadryl. Abdominal attack occurred on 17 Feb 2007. Clinic note does not discuss whether home medications were given. Pt responded after just 15 min, but had a recurrence 5 hours later and went to the ER. ER gave Demerol. Another ER record post trial shows Zyrtec taken from 2 years through present. No other comments as to whether meds taken at home day of attack. No other meds given as per orders at clinic on 17 Feb 2007. Note written after pain resolved states "Adrenaline mi9ght have slowed effect down" [if it had been taken].

Subject -b(6)- has listed current treatments signed 26 Apr 2006 as epinephrine, Winstrol 2 mg qd, and Atarax 10 mg prn. Exclusion criterion 15 marked zero on sheet dated 8/5/06 and on a sheet dated 17 Aug 2005. Conciomitant med shet dated 17 Aug 2005 lists Atarax prn, Winstrol 2 mg qam, Prednisone 5 mg q AM, Tylenol prn, Adrenalin IM prn, FFP PRN, and Benadryl prn, all marked ongoing except prednisone, which was stopped 28 July 2005. Opiates screen collected that day at 15:30 was negative. Note written 17 Aug 2005 at 12:45. Note date of ToS states "no medication at all in the past 4 days…"

Subject -b(6)- has listed on source document Current treatment as Stanazol 2 mg x 3 q AM. Randomization on 20 Aug 2005. Among no and yes boxes, box No for Ezclusion criterion 15 checked. Attack began 6 Aug 2005. Attack became severe unusually quickly. Pt was treated with IV Demerol and epinephrine and discharged 89 Aug with continued mild to moderate pain. Increase in severity fo pain on 19 Aug at 18:00, subsided, then fluctuated spontaneously between 3-4 and 7-8 day of study prior to endrollment, also R back and flnak pain. No comments in note as to what meds taken at home. Also treated in past with FFP 3 units. Study drug resulted in "outstanding improvement" but with persistent back and flank pain. Concomitant medication sheet dated 20 Aug 2005 (day of ToS) lists Stanazol 3 x 2 mg q AM, Pepcid 10 mg po, Zantec (ranitidine), Calcium, Advil, Demerol IV in ER q ~ 6 weeks, Demerol 25 mg tab,and Adrenalin SC, all ongoing except Zantac (stopped 3 weeks ago) and none showing actual stopping date. However, last dose Advil 20:30. Opiate screening report dated 20 July 2005 negative. Undated note states subject discharged at 13:45 (written over). Diary shows complete resolution on 23 Aug at 06:00.

Subject -b(6)- did not have baseline toxicology drawn, as required by the protocol, so the baseline viral safety sample was used per sponsor waiver. It was negative. Current treatment listed as Danocrine 200-300 mg qd. Concomitant med sheet dated 27 Dec 2005 lists only Tylenol 500 mg prn with no start or stop time. Another sheet dated 27 Dec 2005 states "0 meds today – Tylenol…22 Dec & 26 Dec for sinus headache. Pt came to clinic at 11:00 on 27 Dec 2005. Onset of attack was 24 Dec 2005 with waxing and waning. Attack severe enough for treatment acc to patient at8:30 on 27 Dec 2005. No narcotic pain meds in prior week. "Patient has taken no meds to day." Attack resolved 27 Dec 2005 at 13:30. No meds taken at home as per diary.

Subject -b(6)-had current treatment listed as Danazol 200 mg BID (varied dose from 50 to 400 mg on current and previous concomitant med listing), FFP x 1 (none since 2004), Demerol prn since 2003 and Nubane prn in 2004 x 1. Consent signed 29 Aug 2006 at 08:20. Took usual Danazol this AM. Randomization visit sheet also lists Prozac 40 mg qd for OCD and Ibuprofen x 1 last week. At 2 hours 12 min "00:25 – Vistaril 50 mg IM administered L hip for very severe retching, gagging, and some vomiting." Three hours after study medication sheet states "Patient sleepy from Vistaril, but HA continues…Demerol 50 mg IM administered 01:21…01:25 having heaves again – Benadryl 12.5 mg IV given 01:33." "Dramatic improvement sedated & 1 more dry-heaves after the Migraine HA decreased following Demerol + IV Benadryl…which also reduced his belly + back/flank pain significantly." Opiate screen negative (specimen entry date 11/9/2006)."

Subject -b(6)-has an undated Medication (Con-Med) History sheet listing Tylenol prn for pain/HAE, Benadryl caps 25 mg prn for HAE, both started 1995 with no stop date, and Tagamet (cimetadine) prn for HAE started 2000. Note that cimetadine is not listed on the sponsor's PROHMED list of non-permitted and discouraged medications that potentially confound the efficacy analysis. The PROHMED list was used for the sponsor's "Robustness" analysis that adds non-narcotic analgesics to the list of non-permitted and discouraged medications contained in SAP version 2.0. Abd attacl begam at 03"00. worsening at 14:00. Subject arrived at the clinic at 16:35. Consent signed on 29 May 2006 at 16:47. Exclusion criterion 15 box checked no. No change listed on Randomization sheet for medical History Changes. SD with space for randomization number states "0 nothing new since screening" under current and previous concomitant medications. The same 3 meds are all listed as continuing with no stop date on another sponsor-printed Concomitant Med sheet. SD states under Current treatment [for HAE] "Tagamet (crossed out and replaced with Zantec) for stomach – feels this helps." Screening/Enrollment SD states Benadryl dose as either 25 or 50 mg prn, plus Tylenol and Tagemet/Zantac. Diary card has question left black "Did you take any medication?," but has "none" written on another undated page. No SD specifically address -5 hours through ToS.

Subject -b(6)- has a SD dated 26 April 2005 [error?] stating current treatment "0." Randomization SD states took Advil June 7-8…Last night (June 11) mild belly pain. Marked worsening by 5:30 – 6 AM…Called office approx 0700 -→ advised to come in.

Consent signed 12 June 2007 at 09:00. Exclusion criterion 15 box marked no. SD list of current and previous concomitant meds lists Atarax 25 mg prn started 2000 and Hyoscyamine 0.125 mg SL prn started 2000, Depakote (divalproex) 500 mg qd x past 10 days, Trazodone 50 mg prn po since Oct 2006, and Elavil 25-75 mg prn since Dec 2006. Opiate screen urine negative on specimen collected 12 June 2007 at 9:45. Diary shows Ibuprofen 200 mg taken from 13 June through 15 June 2007. No submitted SD addresses whether meds taken from -5 hours through ToS.

Subject -b(6)-SD dated 7 Aug 2007 lists none for current [HAE] treatment. Consent signed 7 Aug 2007 at 9:54. An undated Medication (Con-Med) History sheet lists Benadryl 25 mg prn since 1993 for allergies, Danazol 50-100 mg BID for HAE since 2005, stopped 2006, creatine, and Advil prn for general pain, start unk, no stop date. Onset of abd symptoms on 11 Sept 2007 at 11:30 with additional symptoms at 14:00. SD lists "none" for Medical History Changes/Additions since screening. Opiate screen urine negative on 11 Sept 2007 at 16:45. Diary card for period after discharge lists Advil 400 mg x 1 on 12 Sept 2007 for Dentist appt. No SD address whether meds taken -5 hours to ToS.

Subject -b(6)- took Phenergan 25 mg start 18 Apr 2006, stop 19 Apr 2006, with time written over without initials or date of change (16:30 or 18:30). Note dated 18 Apr 2006 states pt called at 5:58 with abdominal symptoms that started after midnight and became moderate at 5 AM. Tel f/u note dated 19 Apr 2006 states recurrent nausea, severe that persisted until the next morning (today), and moderate swelling of torso. Pt went to ED [Emergency Dept.]. Consent signed 18 Apr 2006 at 7:50 (struck out and initialed). Final Assessment sheet states discharged at 11:00 on 11 Jul 2006. Rescue therapy not given. Concomitant med sheet recording meds from randomization through day 7-9 lists phenergan 25 mg prn ongoing with stop date 27 Apr 2006, Darvocet prn start date 2002, ongoing, with stop date 27 Apr 2006 and phenergan 25 mg prn start date 18 April at 18:30 with stop date 19 April 2006.

Subject -b(6)- has a Concomitant Medications sheet dated 14 Aug 2006 listing Oxandrin 5 mg po qd, started 2002 with stop date 15 June 20056, Zofran 8 mg IV qd starting 3 June 2006 at 9:30 and ending the same day and 4 mg starting 4 June 2006 and ending the same day, Morphine 2 mg IV start date 3 June 2006 at 10:00 ending the same day, Demerol 50 mg po qd starting 4 Jun 2006 and ending the same day, Winstrol 2 mg BID starting 16 June 2006 ending 22 June 2006, and Winstrol 2 mg po qd starting 23 June 2006, continuing with no stop date. Undated sponsor-printed source document shows Exclusion criterion box 15 checked no. Prescriber's Orders sheet shows order for Zofram and morphine dated 3 June at 09:15. Undated progress note from Immunology showing a time of 3:15 AM states subject had ~ 3 hours of abdominal symptoms. Note does not address any home meds.

Subject -b(6)- Baseline sheet shows Consent "Not done." Screening consent had been obtained 3 Aug 2005. Randomization requested 20 Oct 2005 at 07:45. Baseline urine opiates negative. ToS was 20 Oct 2005 at 8:29. Concomitant med sheet dated 20 Oct 2005 bears note "Subject verifies not taking any pain or anti-emetic prior to

treatment/within 4 [circle superscript] post dose" and lists Tylenol x 1 with a stop date of 18 Oct 2005, Allegra 180 mg po qd start 7 Oct 2005 ending 2 May 2006 (date changed from 15 Nov 2005), and Tylenol prn start date 9 Oct 2005 with no time or stop date. No meds listed on diary card.

Subject -b(6)- Baseline sheet dated 13 Dec 2005. Randomization requested 13 Dec 2005 at 10:45. Onset of attack 13 Dec 2005 at 03:33, becoming severe at 06:30. ToS 13 Dec 2005 at 11:19. Concomitant med SD dated 13 Dec 2005 has an annotation dated the following month on 11 Jan 2006 which reads "Subject stated at time of attack she had not taken any anti-emetics or had any conmed changed." The sheet lists Danazole 200 mg po prn from 1999 stop date 22 Jan 2005 and Phenergan 25 mg prn start date 2004, no stop date or time.

Subject -b(6)-- baseline sheet dated 17 Mar 2006. No rescue med given. Urine opiates neg on 17 mar 2006 at 07:04. ToS 17 Mar 2006 at 7:36. Attack resolved 18 Mar 2006 at 8:00. Undated randomization/enrollment sponsor-printed source document (SD) lists as Prior/Concomitant meds Oxandalin 5 mg qd from 2002, Campral (acamprosate) 999 mg po qd for alcohol withdrawal from Jan 2006 with stop date 24 Mar 2006. Prilosec OTC 20 mg po qd starting 15 Feb 2006, continuing, no stop date, and Campral 1998 mg po qd started 24 Mar 2006. No med SD covering – 5 hrs to ToS submitted.

Subject -b(6)- infusion checklist dated 14 April 2006. Rescue med not given. Consent signed 14 April 2006 at 10:15. No new meds listed on Medical History Changes/Additions since Screening. Abd attack began 13 April at 8:00, worsening at 8:30. ToS was at 11:26. Randomization/Enrollment list of current and previous concomitant meds includes Alka-Selzer-Cold 2 tab prn 26 Mar 2006 and Medent DM 2 BID 14 April through 19 April 2006.

Subject -b(6)- on screening/enrollment SD states current maintenance therapy for HAE as palliative for pain of attack only (Darvocet, Vicodin, Phenergan). Attack onset 24 June 2006 at 18:00, becoming moderate or severe the next day at 8:00. Urine tox xcreen negative 25 June 2006 at 11:24. ToS was at 11:54, date not recorded on SD. Attack resolved 26 June 2006 at6 14:00. No meds listed on diary sheet. Randomization/Enrollment Concom med sheet (day of randomization through day 7-9) lists meds including Lexapro (escalopram, SSRI) qd start date 01 June 2006 stoop date 30 Sep 2006, Xanax prn, Darvocet prn, Vicodin prn, Phenergan prn, and Caltrate BID. Ongoing checks for Darvocet, Vicodin, and Phenergan crossed out and initialed but change not dated. Stop dates for the latter 3 indicated as 23 June 2006.

Subject -b(6)- Screening SD states re Current HAE treatment "none/palliative during attack (e.g., Benadryl, advil, etc.). Also noted are Pepsid AC for HAE. Pt had facial attack noted on SD dated 7/10/2006, but note says photos of facial edema attack taken 2 Jul 2006. Another undated Randomization visit SD sheet states Benedryl q hs from 4 Aug ongoing for HAE prophylaxis, Ibuprofen prn for HAE from 2000, ongoing, Pepcid AC for HAE abd symtoms, continuing, and Gas-X prn for upset stomach and

HAE. Subject had abd attrack onset 31 Jul 2006 at 6:30, worsening to moderate or severe at 14:30. ToS at 17:50 on undated SD. Diary card states meds taken at home after discharge. "Subject states having taken no prohibited meds prior to start of attack." [Note that subject may not have understood Benedryl or Ibuprofen to be prohibited.]

Subject -b(6)- Randomization/Enrollment SD notes severe abd attack onset 12 Sept [2006] at 3:05, increasing to moderate or severe at 7:00. ToS was at 8:06 on undated SD. Ab pain continuing at 4 hours. Pt requested rescue medication (2nd dose). Randomization visit SD lists Danazol 100 mg weekly since 16 Aug 2006 (prior tose 100 mg daily), Aleve prn from Jan 2006, Benadryl 25 mg prn since 1987. In different writing intensity appears a note "Subject states she has not taken any medications since start of attack or increased steroid use." Diary card lists Diazepam 5 mg qd on 15 Sept 2006 time not noted, Naproxen for headache on 16 Sept and 20 Sept 2006. Attack ended 12 Sept 2006 at 12:41.

Subject -b(6)- current and previous meds on undated screening/enrollment SD are listed as Winsterol 2 mg qd from 2001 through 3 Mar 200-4 and Stanozolol 1-2 mg po prn from 3 Mar 2004 for HAE. Randomization sheet states "Subject reported having taken no prohibited con meds prior to … attack. Exclusion criterion 15 box checked. Pepcid AC 2 tabs taken 10/8/05 prn indigestion on Randomization visit SD. Another sheet has "Ongoing" box check crossed out, dated 12/9/06 (14 months after ToS!) , and initialed. Pt had mod abd attack onset 9 October at 23:00, worsening to severe 10/11/2006. Order for study med at 10:45 (undated). Opiate test done 10:18 on 11 Oct 2006. ToS 11:12 on undated sheet. Randomization through day 7-9 concomitant med sheet lists also Allegra prn from 2001, ongoing, Epipen prn from 2000, ongoing, no stop dates

Subject -b(6)- baseline sheet dated 11/9/2006. Rescue Medication sheet dated 10 Nov 2006 states rescue med not needed. Consent signed 9 Nov 2006 at 22:25. "…no changes since screening other than HAE attacks…" Exclusion criterion 15 box checked. Randomization/Enrollment SD states "Subject states no current meds taken; takes Danaaol 200 mg po prn. HAE attack onset 9 Nov 2006 at 21:30, worsening at 22:30. Symptoms were intermittent. Abdominal PE lists only symptoms, no exam findings. ToS was at 23:55. Query form dated 14 Jan 2009 confirms no Danazol taken by subject from -5 hours to complete resolution of attack.

Subject -b(6)- undated Screening/Enfollment SD states Current maintenance therapy for HAE consisted of Danazol 200 mg QD (from Jun 2000), Phenergan 25 mg prn (not since early Feb 2006 attack). Another Screening/Enfollment SD also lists htn meds. Changes since screening stmt on SD states Danazol discontinued on 6 Nov 2006 (date changed from 30 Oct 2006). HAE attack began 18 Nov 2006 at 02:00, worsening at 06:00. Symptoms were intermittent. ToS was at 10:26. Diary card shows no meds taken post clinic phase of trial. No submitted SD assesses whether phenergan may have been taken from -5 hours through resolution of attack.

Subject -b(6)- Screening/Enrollment SD lists Current maintenance therapy for HAE as Oxandrin 1.25 mg qd from June 2003. Screening/Enrollment SD lists Current and previous concomitant meds including Yasmin Mar 2006, Oxandrin/Danazol/Stanozolol, Phenergan, Zofran, Toradol, Klonopin, Benedryl/Epinephrine (12/11/06). Consent signed 8 Dec 2006 at 23:45. Note states subject treated open-label for hand swelling due to HAE on 17 Nov 2006. SD for randomization through day 7-9 lists among prior/concomitant meds Yasmin, Astelin, Klonopin (all 3 begun pre-study and continuing with no stop date), plus Theraflu, Advil, Aleve, Benadryl (started 12/11/2006) , and Sinutuss DM begun post-trial during f/u period. Unsigned, un-initialed, and undated statement on Randomization Visit SD states no con med changes "Subject denies taking any prohibitive medication from beginning of attack and to be discouraged during the first four-hours." Study med begun at 00:48. Note dated 12/11/2006 also states "No conmed or changes to previous meds."

Subject -b(6)- signed screening consent 16 Nov 2005. Current maintenance therapy for HAE listed as none. Current and previous concomitant med listed on Screening/Enrollment SD as Advil prn monthy for menstrual cramps. 2nd consent signed 8 Jan 2007 at 11:08. "No changes to med hx since screening other than 3 HAE related attacks." Randomization Visit SD states "Advil prn has not taken any since 1/5/07. Subject confirms not having taken any prohibited meds since beginning/onset of attack (to include narcotic pain med or anti-emetics)" in undated unsigned note on Randomization Visit SD. Advil prn since 1994 listed as Ongoing with no stop date. No meds listed on diary card.

Subject -b(6)- was screened on 26 Aug 2005. Randomization consent signed 12 Feb 2007 at 21:20. Current and previous concomitant meds listed include Oxandrin 2.5 mg qod and Wellbutrin 300 mg qd. Onset abd attack on 12 Feb 2007 at 18:00, worsening at 19:00. ToS was at 22:03. Day 7-9 SD states subject reported on diary no new AEs but documented taking maintenance medication in error as this was previously captured as existing con-med. [Reviewer comment: This statement does not seem to make sense, but the diary card states start date of Oxandrin was 2/07.] Randomization/Enrollment SD prior/concomitant med sheet lists meds including Oxandrin 2.5 mg qod starting in 2001 and changed to 2.5 md q 3 days on 21 April 2007, and Welbutrin XL begun in 2006 and continuing.

Subject -b(6)- has undated sheet listing Seroquel QD ongoing, Risperdal QD ongoing, Cogentin (benztropine, an anti-emetic listed in the *dataset PROHMED.xpt)* **1 mg qd, Benadryl 25 mg prn HAE attack [since] 2003, ongoing, and atenolol. Consent form reviewed by subject on 4 Nov 2006 and signed 6 Nov 2006 and 6 Apr 2007. None listed for current maintenance therapy for HAE. Subject has moderate schizophrenia, "highly functioning" on medication. Exclusion criterion 15 box checked. Randomization SD states no changes from screening. "Confirmed subject has not taken any prohibitive meds (i.e, Benadryl, etc.) since onset of this attack." Facial attack onset 6 April 2007 at 09:00, worsening at 12:00. ToS at 14:38 and at 18:48. Pt noted after several days echyumoses and erythematous ring at all sites were**

IV placed or attempted. Randomization through day 7-9 Conncomitant med SD lists meds including Tylenol 500 mg start date 12 April 2007, Seroquel, Risperdal, Cogentin, and Benadryl 25 mg po prn, all started prior to study and continuing except Tylenol. Only Tylenol shows stop date. No SD submitted addresses what concomitant meds were taken at what time on the day of randomization.

Subject -b(6)- Signed a consent at the screening visit on 16 Nov 2005. Current maintenance therapy for HAE listed on Screening visit form as Danazol 200 mg qd. Randomization SD bears statement that consent signed 3 May 2007 and states "Subject has discontinued daily regimen of Danazol 200 mg. Is now taking this medication on an as needed basis as of Feb 07." Current and previous concomitant meds listed on Randomization visit SD as Danazol Feb 2007 <<arrow>> HAE prophylaxis 200 mg prn po with no statement as to when last taken and Claritin 14 Apr 2007 (last date: 01 May 2007). Attack began 3 May 2007 at 08:00 and worsened at 18:30. ToS was 22:43. Visit day 7-9 SD states "…con meds taken." Randomization/Enrollment SD lists danazol 200 mg po qd changing to prn Feb 2007 and continuing, Claritin 10 mg prn start 14 April 2007 and continuing, and Tylenol 500 mg prn on 4 May 2007. No SD addresses meds that may have been taken in clinic other than study med.

Subject -b(6)- diary states no concomitant meds taken after discharge. Opiate screen negative from 14 Sept 2006. Consent signed on 23 June 2006 and 14 Sept 2006 at 19:45 (day changed without initials or date of change). Exclusion criterion 15 box checked. Current maintenance therapy for HAE listed on Screening SD as Vicoprofen prn for pain – Does not take often. Started 4/3/2006. "Only medication taken is Vicoprofen. Randomization visit dated 14 Sept 2006 and initialed states "No changes" under medical history/additions since screening and states "Has take 0 meds today. Randomization through day 7-9 SD prior/concomitant med sheet includes Vicoprofen po prn started prior to study and ongoing.

Subject -b(6)- consent signed 7 July 2006 and 4 Oct 2006 at 8:30. Screening SD states current maintenance therapy for HAE is 1000 U of C1-INH prn, however nothing listed under current and previous concomitant medication on same Screening sheets. No changes/additions since screening on Randomization SD. Concomitant med review note states last C1-INH treatment about 2 weeks ago…Pt stated that she hasn't taken anything over the last." Pt took Tylenol for headache on 5 Oct 2006. The Prior/Concomitant med SD covering randomization through day 7-9 lists Alessse (OC) 1 po qd from 2003 ongoing, no stop date for "other."

Subject -b(6)- took Celecoxib according to the data listings, start date unknown. No SD were provided.

Subject -b(6)- consented to day (apparently outpatient) "hospitalization" treatment on 01 August 2006 for abdominal HAE attack. Pt had on admission severe abdominal pain, abd spasms, vomiting, nausea, abdominal tenderness, and edema on R face, but attack severity was rated moderate. Exclusion criterion box 15 checked (meaning no).

Concom. Med listed as tranexamic acid BID. Onset of primary symptom was 01 Aug 2006 at 14:00. The attack became moderate/severe the same day at 17:00. Pt had no troubles as of 9 Aug 2006, but later that day, mild abd pain recurred, then subsided entirely at 8:25 PM. "The patient negates taking analgesics, including narcotics and codeine, on the day of the attack on 01 Aug 2006 and on the pre ceding days. She regularly takes tranexamic acid 2 x 400." (Ongoing). Rescue medication was not given. She was discharged at 12:40 AM on 2 Aug 2006. The boxes were not marked as to whether the attack regressed completelyThe "Data Clarification Form" states that tranexamic acid was started 06 Apr 2006. The form also states "If start date not known, could you confirm that medication started prior to 5 h before start of study medication?" Note that the question is not worded with equipoise.

Subject -b(6)- consented for 1 day "hospitalization" at the ----b(4)---------- ---------- on 30 Oct for abdominal pain since 29 Oct. Pain became moderate at 4:20 PM on day of admission. "Today the patient did not take any Danazol [translation]." ToS was 8:34 PM. The subject was discharged at 12:40 AM. After completing treatment the abdomen was "soft, not painful, negative symptoms." Concomitant med was "Danazal" 400 mg prn study indication [HAE] started prior to study and ongoing. Exclusion criterion 15 box checked. Rescue med was not given. The diary question "Did the abdominal or facial HAE attack regress completely?" was not checked yes or no. The data clarification form dated 14 Jan 2009 confirmed that the subject did not take Danazol between 5 hours prior to study drug infusion and 24 hours thereafter.

Subject -b(6)- consented for 1 day "hospitalization on" 18 June 2007. Pt started the androgen Stanazolol 2 mg/day for prophylaxis on 22 May 2007. Exclusion criterion 15 box checked. ToS was 18 June 2007 at 12:43. Pt discharged ~ 4 hours later, but date and time of discharge left blank. HAE attack had not resolved as of discharge. Pt had slight pain and spasms, both of which had improved. Pt diary does not show end of symptoms of HAE attack day or time, but box is checked that other drug(s) were taken.

Subject -b(6)- consented for participation on 6 Dec 2006 at 19:45. Box checked for Exclusion Criterion 15. Concomitant med was Exacyl (tranexamic acid) 2 x 1 tab qd. Diary states that symptoms abated completely on 9 Dec 2006 at 18:00. No meds taken post discharge. ToS was 6 Dec 2006 at 20:34. Rescue med was given, but it's date and time were left blank. Discharge was listed as 7 Dec 2006 at 1:40 and at 7:00 (~ 5 hours after last infusion). Box not checked as to whether abdominal or facial HAE attacks regressed completely. Pt had mild pain and mild spasms on discharge, both improved from pre-treatment. INDIVIDUAL MEDICAL ORDER CHART for the --b(4)-------- ---------- (translation) shows 500 mL saline + 2 amp "NO-spa" to help sleep ordered 6 Dec "Day," 19.2 mL study medicine at 9:10 PM the same day, and a 2nd 19.2 mL of study medicine on 7 Dec "Day," Exacyl 2 x 1 x 500 mg, Modafen 200 mg QD stopped 5 Dec 2006, Ibuprofen + prenolozfladyne 80 mg IV QD starting 9:50 PM on 06 Dec 2006.

Subject -b(6)- was entered on 17 April 2007 at the "---b(4)----------" with stomach ache, N & V. HAE symptoms started around 11 AM and increased to severe at 13:30. Patient took 1 tabs of No-spa and 2 tabs of Danazol at home in the Morning. Consent was signed that day at 20:00.On that day the patient was prescribed day and night 500 mL saline plus 1 ampule of a medicine equaling 0.5 g in 5 mL, as well as 2 x 18.2 mL of study medication. Among concomitant medications listed on the diary, the earliest was begun on 21 April 2007. Exclusion criterion 15 box checked. Concomitant meds listed on sponsor-printed "source documents" included Danazol with a start date of the day of enrollment and an end date the same, as well as "NOSPA" (Ibuprofen + prenolozfladyne) x 1 on 17 April 2007, time not noted. A Data Clarification Form created 14 Jan 2009 states "Patient uses Danazol only to treat HAE..Patient took Danazol only on 17 Apr 2007 previous dose of Danazol at 2006." ToS was 17:01. The translation of the documents is grossly incomplete.

Subject -b(6)- treated in -b(4)-, had a ToS was 21 Oct 2006. The sponsor's query form regarding concomitant med use from -5 hours to 24 hours was sent on 13 January 2009. The physician stated that the subject took ASA 100 mg daily since 1001 at 14:00. ToS was stated to be 14:00, at which time the subject had tongue edema and dysphagia, but there was no information in the clinical history or CRF about the intake of ASA. A diary was not provided on discharge because "the protocol of the study established it was not necessary to give the patient the "Patient diary" if he was completely free of symptoms." The physician and another physician to initially attended the patient indicated they did not "think" the patient took ASA on 21 Oct 2006, but he stated "Nevertheless, two years after the study drug administration is very difficult to be sure about data not registered in the clinical history, neither in the CRF, as at that moment there was no document to fill in with the data required now." The subject was symptom free at discharge at 18:15. No source documents from the day of treatment were included except the discharge physical sponsor-printed page.

Note that for subject -b(6)-, sponsor's table Q5B3b failed to include Demerol 50 mg IV/PO prn (HAE or arthritis) in the table, yet this was included on the CRF and on notations on source records. The patient received a waiver for entry by the sponsor despite a positive opiate and hydrocodone test results in the local lab at baseline by -b(4)-. The central lab was negative by -b(4)-. The source documents (diary) also state that Loratab (hydrocodone) was taken on 15 through 17 August for headaches on the 1st 2 days and arthritis on the 3rd day. Soma was also taken on 14 Aug for arthritis. The diary also states that 0.3 cc of epinephrine was also taken prn for HAE (no dates indicated). No hospital medication record per se was included in the source documents provided by the sponsor. According to physician notes, attack began on 13 Aug ~ 6 PM. He was given Vistaril 25 mg at 1:20 AM on 14 Aug 2005, after the attack began, which is 1 hr 15 min prior to ToS. Yet, contrary to these "source documents," the CRF box was chedked "no" for exclusion criterion 15: "Narcotic pain medication and/or anti-emetics between start of attack and administration of study medication." The test product was begun on 14 Aug at 2:35 AM. Most recent FFP was 25 May 2005. Pt received rescue dose of study med at 7:15 AM. This

subject will be given a "poor/failure" imputation of 24 hours in the FDA primary endpoint analysis, due to administration of the anti-emetic, hydroxyzine within the 5 hour time window prior to ToS.

Subject -b(6)- attack actually began 14 days prior to his readmission to hospital. He was given Demerol during his 1st hospitalization, which contradicts the answer to inclusion criterion 15. The patient developed hoarseness prior to admission. ToS 18:30 (written over without initial of recorder) on 20 Aug '05. Outstanding improvement in pain. Trace hemoglobin on urinalysis on discharge. No "standard" hospital medication records per se were included in source documents provided by sponsor.

Subject -b(6)- historically averaged ~ 10 attacks per month. Current treatment is listed as Nanazole 50 mg qd-bid as of sheet completed 21 Feb or July 2005. Handwritten note by exclusion criterion 15: "0 since start of attack. Prior concom meds page completed 15 Sept 2005 lists Effexor XL 150 mg qd started June 2005, ongoing, no stop date, Danazol 50 mg qd, stopped 8 June 2006, Naprosyn 500 mg qd begun 5 July 2006, ongoing, and epinephrine for HAE 1;1000 im 3x per episode, ongoing, not stop date, "last dose 7 Sept 2005." Opiate test neg from specimen collected 15 Sept 2005. Attack resolved 18 Sept 2005 at 6:30 PM. Patient took epinephrine 1/3 mg on 15 Sept 2005 for HAE, according to patient diary, time not note4. Pt arrived in clinic on 15 Sept at 00:05 with HAE attack, and was enrolled in the study and drug was given from 1:45 to 1:55 AM. Pt reported minimal pain relief at 3:35 am, but developed a headache, and requested rescue medication and was administered at 6:10 AM. Symptoms began to improve at 5:40 AM. Pt improved over the next 3 hours and was discharged sometime after 10:15 AM.

Subject -b(6)- had severe nausea and moderate torso swelling at home the day of discharge, after being asymptomatic on discharge. Attack began after midnight 18 April '05 and became moderate at 5 AM. CRF box "Complete resolution within 24 hours?" not marked. Phenergan 25 mg po given 16:30 or 18:30 or 16:30 (written over without date or initials of the person making the change) on 18 April '06 and stopped 19 April '06. On "ZLB Behring CE1145-3001 Day 7 – 9 Source Documentation" sheet the handwritten entries regarding the patient's post-hospital discharge course on 21 April appear ABOVE notes regarding the patient's symptoms of severe nausea on 18:30 on 18 April and 19 April, suggesting these "source document" entries were not contemporaneous but rather a reconstruction after the fact. *No standard hospital medication records per se were included in source documents provided by sponsor.* Rather, a sheet entitled "ZLB Behring CE1145-3001 Randomization/Enrollment Source Documentation" that is similar to the CRF in that it asks the start and stop time of concomitant medications but does not include space for the time of each administration of the medications. No rescue med was given according to ZLB "source documents." The latter provided documents do not stated when ToS occurred.

The Data Query Form for subject -b(6)--- states that Exacyl (tranexamic acid) was increased from 2 x 250 mg daily to 2 x 500 mg daily on 27 Oct 2006. The translation of the clinic record shows the latter to be dated 20 October at 10:26. HAE facial attack began 19 Oct 2006 at 10:00. Pt had edems of "sole" 18 Oct 2006 and had had abdominal pain x ~ 1 week. Exam showed facial edema, mild R episgastric tenderness. ToS at 10:15. No hospital medication records were among the "source documents" provided by the sponsor.

Subject -b(6)-- has a source document on which is listed "ONCE ONLY, PRE-MEDICATION & NURSE INITIATED MEDICINES" which lists C1 Inhibitor Study 18 mL x 2 IV, begun at 12:50 on 11 April. No entries are on the part of the sheet labeled "Medicines Taken Prior to Presentation to Hospital." On 11 April 2007 at 11:15 a nursing/study coordinator noted that the patient presented to the ER for randomization and tox screen was negative. Symptom includes rash, abdominal pain & swelling and nausea & vomiting. "Patient has not taken any concomitant medications." Exclusion criterion 15 box checked. Sponsor-printed source document lists Danazol 100 mg daily as concomitant medication.

Subject -b(6)-, a facial attack subject, had a negative tox screen on entry. The HAE attack began at 18:00 hours on 24 June 2006 and the subject was entered at 8 AM on 25 June 2006. Study medication was begun at 11:54 AM on 2 June 2006. Records provided by sponsor do not show times or dates prn medications, including Xanax (alprazolam), Darvocet (prophoxyphene, Vicoden (contains hydrocodone), or Phenergan (promethazine) were given. The box "Ongoing?" was checked or all 4 medications, but was crossed out and initialed but without the change being dated for the latter 3 meds. The end date of the latter 3 meds was listed as 23 June 2006, the day prior to onset of the attack. Discharge document shows no symptoms. The last page of the diary which would record concomitant meds is not readable due to the original color being dark orange, but it is stated that no meds were listed.

Subject -b(6)- has a Parexel document stating that 40 pages of SD [source document] worksheets in English plus 5 in Hebrew were provided with a partial translation of page 2. "No information regarding concomitant medication in the requested time range is provided in all other (1,3,4,5) pages." The diary listed medications taken > 24 hours from the "injection time." The subject arrived on 10 Sept 2007 at 10:50 AM. Consent was signed 8 days previously. Box checked for Exclusion criterion 15. Concomitant med: "Takes Tramadol and Ocycod occasionally." Pt enrolled with severe abd pain. Attack began 10 Sept 2007 at 9:00 and became severe at 9:45. Study med ordered 11:25. Tox screen negative. ToS = 10 Sept 2007 at 11:55. At 2 hours following ToS pt worsened with diarrhea changing from severity 2 to 3. Subject had no relief through 4 hours. Pt was given the anti-emetic IV phenergan at 1:45 hours, but nausea and pain persisted. Rescue medication given as subject was non-responder. Pt discharged at 20:10 at which point he "feels good." At 5 hours, abdominal symptoms were still moderate intensity, but pain, nausea, and cramps were better and primary endpoint question marked "yes." At 7 hours only mild

cramps remained. All symptoms resolved as of 20:00. "Oxycode" was taken the day following discharge and Berinert was given 3 days after discharge.

Subject -b(6)- (low dose group) took Danazol 200 mg qod. Study drug given at ¼ of prescribed protocol rate. The diary was not received by the study site. Resolution date and time of HAE attack were missing. Outpatient progress noted dated 29 Oct 2005. Pt also treated with Winstrol 2 mg but it seems this was changed to Danazol qod begun "> 6 months" (30 Aug 2005, according to Data Clarification Form dated 22 Jan 2009).

Subject -b(6)- had blood drawn 28 July 2005 at 12:15. Current maintenance therapy on screening/enrollment sheet listed as Danazol 1 BID since 1991. Randomization/Enrollment Source Documentation (sponsor printed) has Exclusion criterion 15 box checked and states none for current and previous concomitant medications. A note states no androgens since early Aug. The Data Clarification Form was signed 22 Jan 2008. Randomization visit sponsor-printed source document has initials dated 21 Dec 2006. No stop date was indicated for Danazol.

Subject -b(6)- HAE attack resolved completely on 10 June 2006 at noon according to the patient diary card. The card also states that the subject did not take "any medication you take after your discharge from hospital until 1 week later when you return to the hospital for your final assessment." This seems surprising in view of the polypharmacy at screening and the statement that there were "No changes in meds since screening." The tox screen of this subject for the sample taken on 6 September 2005 at 10 AM was negative for opiates at the central lab of ----b(4)---------- ---------- in a report dated 20 November 2006, but was positive for oxycodone at 529 ng/mL, confirmed by -b(4)- at the local lab "---b(4)---------- in the sample taken at 9 June 2006 at 00:00. The screening cutoff for opiates at the local lab was 300 ng/mL The subject was screened on 5/2/2006. The screening form inappropriately asked inclusion criterion 15 (Narcotic pain medication and/or anti-emetics between start of attack and enrollment (signing of informed consent). This was inappropriate because the subject was not having an attack at the time of screening. However, a 2nd undated document containing the exclusion criteria entitled "ZLB Behring CE1145-3001 Screening / Enrollment Source Documentation" also has exclusion criterion 15 checked "no." A similarly entitled sheet is marked "No changes in meds since screening." No documents provided for this subject bear the name of any hospital. The only sheet listing medications, entitled "CONCOMITANT MEDICATION," is marked at the top "ZLB Behring CE1145_3001" and states at the top "Please document dose, unit, route, frequency, date and time of any drug that was given during the course of the study. No stop times are listed for clonazepam, promethazine, compazine, hydroxyzine, Percocet (which is prescribed QID SINCE 1999, not "PRN" as indicated in the sponsor's table), benadryl, Lortab 10 (Vicodin); however stop dates are listed for 2 administrations of open label C1-INH on 12 and 16 June 2006. Clonazepam was not listed in sponsor Table Q5B3b as it should have been, given that benzodiazepines were listed among the sponsor's list of medications with anti-emetic properties. This subject will be counted as a "poor/failure" in the

FDA analysis in view of the positive ocycodone quantitative determination, confirmed by ----b(4)----------on the day of entry into the trial, as well as the lack of a stop date for the QID ongoing prescription of Percocet in this patient.

Subject -b(6)- Diary Card states that 24 hours after last infusion of study drug was on 19 Oct 2006 at 9:05. Tox screen collected 18 Oct 2006 at 00:00 was negative. Attack had not resolved as of discharge, due to residual mild facial swelling. Photos taken at 4-6 and 20 hrs. Complete resolution on 20 Oct 2006 at 6:10 AM. Inclusion criterion "…attacks necessitating hospital admission…" checked. Exclusion criterion 15 checked. Concomitant meds included Dicyclomine TID for HAE since 2001 with no stop date, Lunesta 3 mg po qd since 2005, stopped 0-illegible/2006, Ambien 10 mg po qd started ~ 03/2006, ongoing and Amicar 2 g QID started 4 April 2006, ongoing. Undated Randomization Soruce Document (Baseline) states has not taken any prohibited medications since start of attack. [Reviewer Comment: This does not mean that subject had not taken discouraged medications since start of attack.]

Subject -b(6)- took no medication on discharge, according to the diary card checkbox. Screening/Enrollment sponsor-printed source document states current maintenance therapy for HAE as danazol (only when on vacations(, phergan supp. 25 mg and Toradol 10 mg prn, times not stated. Consent was signed 18 Jan 2007 at 4:05. and 03 Feb 2007 at 17:50. Exclusion criterion 15 box checked. Medical history since screening states "no medications today" and "Confirmed pt. has not had any narcotic pain meds or anti-emetic" on undated screening/enrollment page. Opiates negative on 3 Feb at 18:47.

Subject -b(6)-received promethazine 25 mg IV at 3 hr 4 min and the table lists no pertinent exclusion criteria or "SDV findings." The latter, according to sponsor explanation made at a 2009 teleconference, refer to review of source documents. Patient Diary Card states that HAE attack resolved 12 Aug 2007 at 8:00. Opiates wer negative at screening, collection date not indicated. HAE attack began at 4 PM with abdominal pain. ER record (not clearly dated, but with different font date of 15 Aug 2007 at 22:10) indicates that Medicatios were Zyrtec and Clorazepam. ER Triage record 8/9/07 at 22:40 shows abd pain and tenderness with meds listed as Zyrtec and clonazepam. Pt given Toradol and phergan at 23:54 IV. Screening Source Doc states Consent signed 12 Feb 2007. Screening/Enrollment source document states 2 mg Stanozol QD, Zyttec, Protonic 40 mg qd, Toradol, Klonazepam and Phenergan. Randomization Source Document states consent signed 9 Aug 2007 at 19:35. Current and previous concomitant medications listed as none, which conflicts with ER sheet of same date. Day 7-9 Source Documentation has note dated 24 Oct 2007 (2.5 months after randomization) stating "Please note…Subject was called to confirm no Zyrtec (PRN) taken from start fo stuidy med dose on 8/9/07 until relief of symptoms on 8/12/07. All meds are listed as continuing with no stop dates on Randomization/Enrollment sponsor-printed sour docuemnt. Stanozolol was listed as PRN.

Subject -b(6)- had exclusion criteria boxes not checked, including box 15, on baseline form; screening/enrollment form had box 15 checked. Attack began at 16:00 or 18:00 (date written over). ToS 22 June 2006 at 9:33. Rescue medication given at 13:40. Pt started to improve at 3 hr 30 min (13:03), but "no change" at 4 hr (13:28). Attack resolved at 17:10. Note states ibuprofen prn started 3 days ago. Took x 2 days (illegible) on Randomization/Enrollment form. "[Pt.] has not taken any medication for acute relief of this attack." Concomitant meds: Danazol 400 mg qd, Milk Thistle 2 tabs qd, Tigan 200 mg supp prn, last taken ~ 3 nights ago.

Subject -b(6)- screening/enrollment source document states current therapy for HAE is 1000 U C1-INH prn. Current and previous concomitant medication sheet left blank. Randomization source document (baseline) states consent signed 4 Oct 2006 at 8:30 and "last C1-INH treatment about 2 weeks ago. Pt stated that she hasn't taken anything over the last." Telephone notes state attack resolved in < 24 hours. Tylenol for headache given 5 Oct 2006. Another Randomization/Enrollment Source Documentation sheet lists 3 concomitant meds, including Alesse 1 tab qd since 2003, ongoing, Tylenol, as noted above, and Gravol 1 tab prn started Dec 2006. This is an example of either the wrong form being used or the forms being filled out much later, as Dec 2006 is 2 months after randomization. Data from 2 months after randoimization should not be filled out on a "Randomization/Enrollment" Source Documentation page.

Subject -b(6)- records indicate (translation) the subject had abdominal cramps starting at 2 Aug 20078 at 5:00, w3orsening at 9:45. The subject was admitted to the hospital. Treatment was Exacyl (tranexamic acid) 2 x 500 mg PO as prophylaxis "in the same ongoing dose." The subject was enrolled on 2 Aug 2007, time not noted, and discharged "in a good health condition" with the documented time indicated as 18:30. ToS was 2 Aug 2007 at 14:20. The subject had no symptoms at discharge. Subject received 500 U of Berinert P on 8 Aug 2007. <u>No hospital medication records were provided</u>.

Subject -b(6)- Berinert P, on therapy Exacyl 500 mg ½-0-1/2. The last page of the diary card was not readable, due to the original having a dark orange color,a ccording to a printed statement, which asserts that "This NTF is to document/confirm that no concomitant medications have were listed in the patient diary." This statement is dated 8 April 2009 and is signed by a Czech Clinical Monitor, who also provided the translation of the brief Progress note for this facial attack. No concomitant medication sheet covering the prior prior to treatment or the treatment period was included in the Czech source documents provided. ToS was on 4 Dec 2006 at 8:50.